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(71) Applicant : **MERCK & CO. INC.**
126, East Lincoln Avenue P.O. Box 2000
Rahway New Jersey 07065-0900 (US)

(72) Inventor : **Fisher, Michael H.**
RD 1, Old York Road, Box 302
Ringoes, NJ 08551 (US)
Inventor : **Wyvratt, Mathew J.**
1130 Puddingstone Road
Mountainside, NJ 07092 (US)
Inventor : **Schoen, William R.**
6 Maryellen Drive
Edison, NJ 08820 (US)
Inventor : **Devita, Robert J.**
1490 Lamberts Mill Road
Westfield, NJ 07090 (US)

(74) Representative : **Thompson, John Dr. et al**
Merck & Co., Inc. European Patent Department Terlings Park Eastwick Road
Harlow, Essex CM20 2QR (GB)

(54) Novel benzo-fused lactams that promote the release of growth hormone.

(57) There are disclosed certain novel compounds identified as benzo-fused lactams which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to increase the stature of those afflicted with a lack of a normal secretion of natural growth hormone. Growth promoting compositiors containing such benzo-fused lactams as the active ingredient thereof are also disclosed.

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BACKGROUND OF THE INVENTION

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic process of the body:

1. Increased rate of protein synthesis in all cells of the body;
2. Decreased rate of carbohydrate utilization in cells of the body;
3. Increased mobilization of free fatty acids and use of fatty acids for energy.

A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering an agent which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recently, recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray.

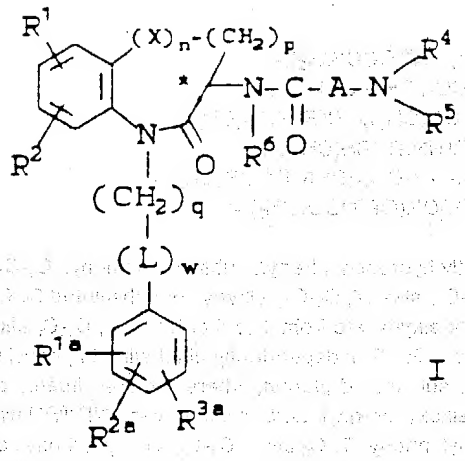
Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low. The instant compounds are non-peptidyl agents for promoting the release of growth hormone which may be administered parenterally, nasally or by the oral route.

SUMMARY OF THE INVENTION

The instant invention covers certain benzofused lactam compounds which have the ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food production where the stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe the benzofused lactam compounds. It is a further object of this invention to describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe compositions containing the benzo-fused lactam compounds for the use of treating humans and animals so as to increase the level of growth hormone secretions. Further objects will become apparent from a reading of the following description.

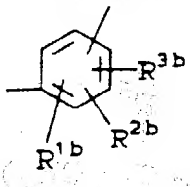
DESCRIPTION OF THE INVENTION

The novel benzo-fused lactams of the instant invention are best described in the following structural formula I:

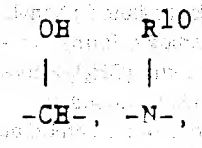


I

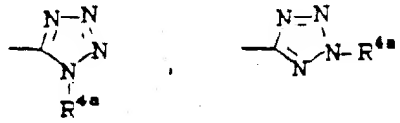
where L is



n is 0 or 1;
p is 0 to 3;
q is 0 to 4;
w is 0 or 1;
X is C=O, O, $S(O)_m$,



-CH=CH-;
m is 0 to 2;
R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_3 perfluoroalkoxy, $-S(O)_mR^{7a}$, cyano, nitro, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;
R^{7a} and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the phenyl substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy and v is 0 to 3;
R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9 or phenoxy substituted with R^9;
R^9 is



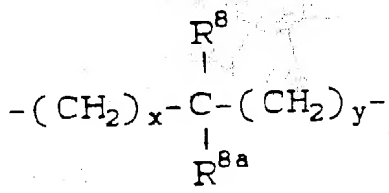
$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-,
$R^{7b}CO(CH_2)_v$-, $R^{7b}O(CH_2)_vCO$-, $R^4R^5N(CH_2)_v$-,
$R^{7b}CON(R^4)(CH_2)_v$-, $R^4R^5NCO(CH_2)_v$-, $R^4R^5NCS(CH_2)_v$-,
$R^4R^5NN(R^5)CO(CH_2)_v$-, $R^4R^5NN(R^5)CS(CH_2)_v$-,
$R^{7b}CON(R^4)N(R^5)CO(CH_2)_v$-, $R^{7b}CON(R^4)N(R^5)CS(CH_2)_v$-,
$R^4N(OR^{7b})CO(CH_2)_v$- or $R^{7a}CON(OR^{7b})CO(CH_2)_v$-;

and v is as defined above;

R^4, R^{4a}, R^5 are independently hydrogen, phenyl, substituted phenyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, C_3-C_{10} alkenyl, substituted C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, or substituted C_3-C_{10} alkynyl where the substituents on the phenyl, alkyl, alkenyl or alkynyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, phenyl C_1-C_3 alkoxy, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, where the substituents on the phenyl are as defined above, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_1-C_6 alkyl, phenyl, phenyl C_1-C_6 alkyl, C_1-C_5-alkoxycarbonyl, or C_1-C_5-alkanoyl-C_1-C_6 alkyl; or R^4 and R^5 can be taken together to form $-(CH_2)_rB(CH_2)_s$- where B is CH_2, O or $S(O)_m$ or N-R^{10}, r and s are independently 1 to 3 and R^{10} is as defined above;

R^6 is hydrogen, C_1-C_{10} alkyl, phenyl or phenyl C_1-C_{10} alkyl;

A is



where x and y are independently 0-3;

R^6 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, trifluoromethyl, phenyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, phenyl C_1-C_3 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl,
C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or $-NR^{10}R^{11}$ where R^{10} and R^{11} are as defined above; or R^6 and R^{8a} can be taken together to form $-(CH_2)_t$-where t is 2 to 6; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

In the above structural formula and throughout the instant specification, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

Preferred compounds of the instant invention are realized when in the above structural formula:

n is 0 or 1;

p is 0 to 3;

q is 0 to 2;

w is 0 or 1;

X is O, $S(O)_m$,

-CH=CH-;

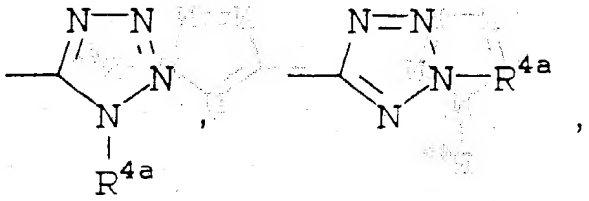
m is 0 to 2;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl; phenyl and v is 0 to 2;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9 or phenoxy substituted with R^9;

R^9 is



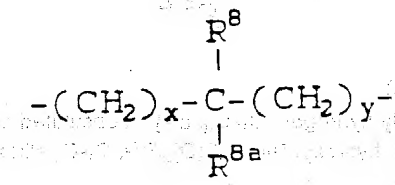
$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-,
$R^{7b}CO(CH_2)_v$-, $R^4R^5N(CH_2)_v$-, $R^{7b}CON(R^4)(CH_2)_v$-,
$R^4R^5NCO(CH_2)_v$-, $R^4R^5NCS(CH_2)_v$-, $R^4R^5NN(R^5)CO(CH_2)_v$-,
$R^{7b}CON(R^4)N(R^5)CO(CH_2)_v$-, $R^4N(OR^{7b})CO(CH_2)_v$- or
$R^{7a}CON(OR^{7b})CO(CH_2)_v$-; where v is as defined above;

R^4, R^{4a}, R^5 are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, phenyl C_1-C_3 alkoxy, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, where the substituents on the phenyl are as defined above, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy or formyl;

R^4 and R^5 can be taken together to form
$-(CH_2)_rB(CH_2)_s$- where B is CH_2, O or $S(O)_m$ or N-R^{10} r and s are independently 1 to 3 and R^{10} is as defined above;

R^6 is hydrogen, C_1-C_{10} alkyl or phenyl C_1-C_{10} alkyl;

A is



where x and y are independently 0-2;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl,
C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hy-

drogen, C_1-C_6 alkyl, or C_1-C_5 alkanoyl-C_1-C_6 alkyl; or R^6 and R^{8a} can be taken together to form -$(CH_2)_t$- where t is 2 to 4; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms; and pharmaceutically acceptable salts thereof.

Additional preferred compounds are realized in the above structural formula when:

n is 0 or 1;

p is 0 to 2;

q is 0 to 2;

w is 0 or 1;

X is $S(O)_m$, -CH=CH-;

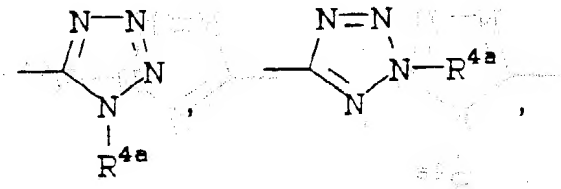
m is 0 or 1;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, -$S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl and v is 0 to 2;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9 or phenoxy substituted with R^9;

R^9 is

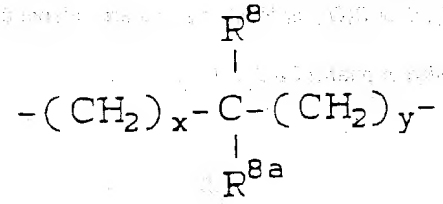


$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-,
$R^{7b}CO(CH_2)_v$-, $R^4R^5N(CH_2)_v$-, $R^{7a}CON(R^4)(CH_2)_v$-,
$R^4R^5NCO(CH_2)_v$-, $R^4R^5NCS(CH_2)_v$-, $R^4N(OR^{7b})CO(CH_2)_v$- or
$R^{7a}CON(OR^{7b})CO(CH_2)_v$-; where v is as defined above;

R^4, R^{4a}, R^5 are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, fluoro, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, where the substituents on the phenyl are as defined above, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy;

R^6 is hydrogen, C_1-C_{10} alkyl;

A is



where x and y are independently 0-2;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl,
C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or R^8 and R^{8a} can be taken together to form -$(CH_2)_t$- where t is 2; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms; and pharmaceutically acceptable salts thereof.

Still further preferred compounds of the instant invention are realized in the above structural formula when;

n is 0 or 1;

p is 0 to 2;

q is 1;

w is 1;

X is $S(O)_m$, -CH=CH-;

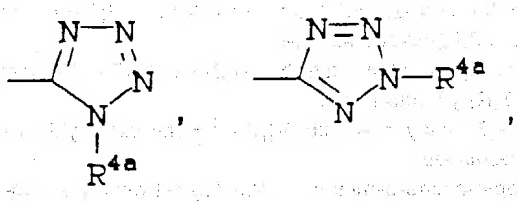
m is 0 or 1;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl, phenyl and v is 0 or 1;

R^{3a} and R^{3b} are independently hydrogen or R^9;

R^9 is



$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-,

$R^{7b}CO(CH_2)_v$-, $R^4R^5N(CH_2)_v$-, $R^{7b}CON(R^4)(CH_2)_v$-,

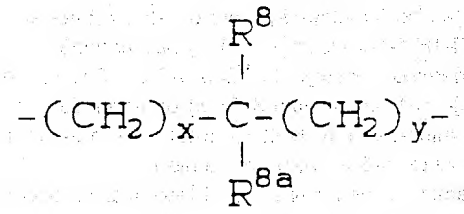
$R^4R^5NCO(CH_2)_v$- or $R^4N(OR^{7b})CO(CH_2)_v$-; where v is as defined above;

R^4, R^5 are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 3 of hydroxy, C_1-C_3 alkoxy, fluoro, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, where the substituents on the phenyl are as defined above;

R^{4a} is hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents on the alkyl are from 1 to 3 of hydroxy;

R^6 is hydrogen;

A is



where x and y are independently 0-1;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl,

C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t$-where t is 2; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms; and pharmaceutically acceptable salts thereof.

Representative preferred growth hormone releasing compounds of the present invention include the following:

1. 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
2. 2(R)-amino-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-propanamide
3. 2(R)-amino-3-phenyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1,'-biphenyl]-4-yl]-methyl]-

1H-1-benzazepin-3(R)-yl]-propanamide
4. 2(R)-amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide
5. 3-(2-hydroxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-[1-(2-hydroxyethyl)-tetra-zol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
6. 3-(2-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
7. 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-propanamide
8. 3-amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
9. 3-amino-3-methyl-N-[7-trifluoromethyl-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
10. 3-amino-3-methyl-N-[6-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
11. 3-benzylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butaramide
12. 3-amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide
13. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
14. 3-(2(S)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
15. 3-(2(R),3-dihydroxypropyl)amino-3-methyl-N-[2,3,-4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
16. 3-(2(S),3-dihydroxypropyl)amino-3-methyl-N-[2,3,-4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
17. 3-(3(S)-hydroxybutyl)amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
18. 3-(3(S)-hydroxybutyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
19. 3-amino-3-methyl-N-[7-hydroxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
20. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-hydroxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
21. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
22. 2-(3(R)-hydroxybutyl)amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide
23. 2-(3(S)-hydroxybutyl)amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl)-1H-1-benzazepin-3(R)-yl]-propanamide
24. 3-Amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl)-4-yl)methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
25. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
26. 3-(3(S)-hydroxybutyl)amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
27. Quinuclidine-N′-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-3-carboxamide
28. 3-(2-fluoropropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
29. 3-(2-methoxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
30. 3-(2-hydroxy-2-methylpropyl)amino-3-methyl-N-[2,-3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
31. 4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,-3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl]-[1,1′-biphenyl]-2-carboxamide
32. 4′-[[3(R)-[[3-[(2(R)-hydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-

benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide

33. 4′-[[3(R)-[[(3-[(2(S),3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide

34. N-ethyl-4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1-biphenyl]-2-carboxamide

35. N-ethyl-4′-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)-amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetra-hydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide

36. N-methyl-4′-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)-amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetra-hydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide

37. 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-hydroxymethyl[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide

38. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-hydroxymethyl[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

39. 3-Amino-3-methyl-N-[2,3,4,5-tetranydro-2-oxo-1-[[2′-aminomethyl[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide

40. 3-(2(R)- hydroxypropyl)amino-3-methyl-N-[2,3,4,-5-tetrahydro-2-oxo-1-[[2′-aminomethyl[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

41. 4′-[[3(R)-[[3-[(2(S),3(S),4-trihydroxybutyl)-amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetra-hydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide

42. 4′-[[3(R)-[[3-[(3-hydroxybutyl)amino]-3-methyl-1-oxobuthyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide

43. 3-Amino-3-methyl-N-[2,3-dihydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide

44. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3-dihydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

45. N-ethyl-4′-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)-amino]-3-methyl-1-oxobutyl]amino]-2,3-dihydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide

46. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2′-(1H-tetrazol-5-yl)(1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide

47. 3-(2(S)-hydroxypropyl)amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide

48. N-ethyl-4′-[[3(S)-[[3-[(2(S),3-dihydroxypropyl)-amino]-3-methyl-1-oxobutyl]amino]-3,4-dihydro-4-oxo-1,5-benzothiazepin-5(2H)-yl]methyl]-[1,1′-biphenyl]-2-carboxamide

49. 4′-[[3(S)-[(3-amino-3-methyl-1-oxobutyl)amino]-3,4-dihydro-4-oxo-1,5-benzothiazepin-5(2H))-yl]-methyl]-[1,1′-biphenyl]-2-carboxamide

50. 4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl]-[1,1′-biphenyl]-2-thioamide

51. N-hydroxy-4′-[[3(R)-[(3-amino-3-methyl-1-oxo-butyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide

52. N-hydroxy-4′-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)-amino]-3-methyl-1-oxobutyl]amino)-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl)-2-carboxamide

53. N-hydroxy-4′-[[3(R)-[[3-[(2(R)-hydroxypropyl)-amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetra-hydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide

54. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide

55. 3-amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl)-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide

56. 3-amino-3-methyl-N-[7-methylthio-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl-]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide

57. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methylthio-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

58. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methyl-sulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl)-4-yl)methyl]-1H-1-benzazepin-3(R)-yl]butanamide

59. 3-amino-3-methyl-N-[7-methylsulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

60. 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(acetylaminomethyl)[1,1′-biphenyl]-4-yl] methyl]-1H-1-benzazepin-3(R)-yl]butanamide

61. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(acetylaminomethyl)[1,1′-

biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl] butanamide

62. 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(benzoylaminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide

63. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(benzoylaminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl] butanamide

64. 3-amino-3-methyl-4-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl)butanamide

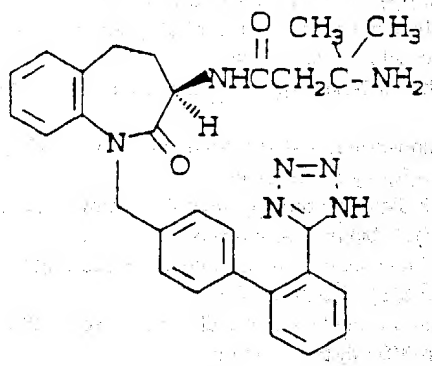
65. 2-amino-2-methyl-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]proparamide

66. 3-(2(R)-hydroxypropyl)amino-3-methyl-4-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H--1-benzazepin-3(R)-yl]butanamide

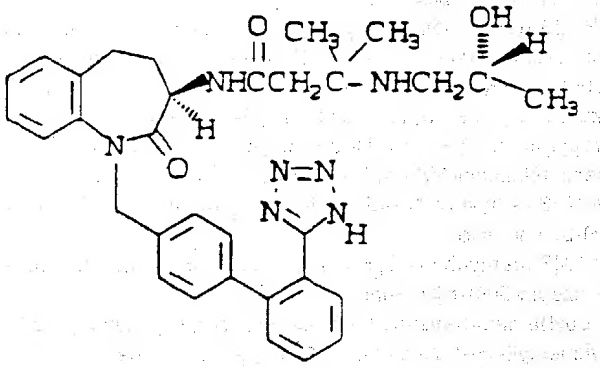
67. 2-(3-hydroxybutyl)amino-2-methyl-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]propanamide

Representative examples of the nomenclature employed are given below:

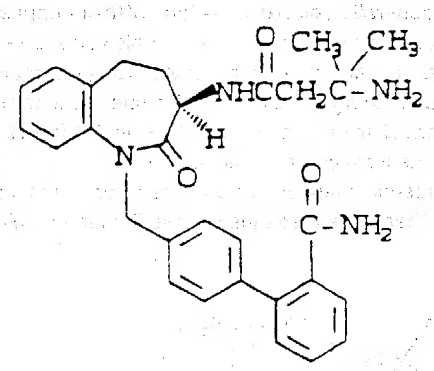
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]butanamide



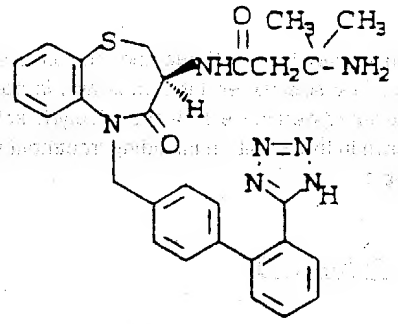
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetra-hydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]butanamide



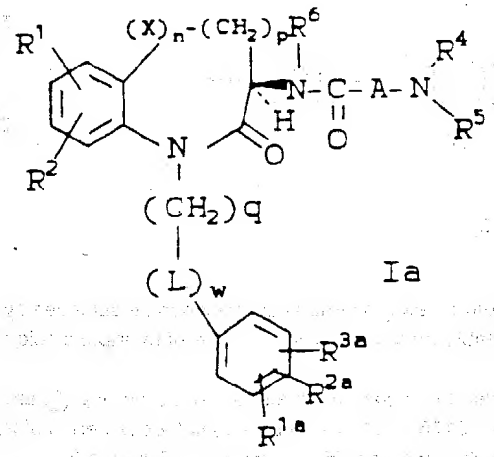
4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,-4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide



3-amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide



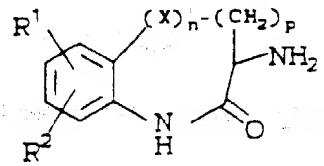
The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in the structural Formula I above. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure optical isomers or racemic mixtures thereof, be included within the ambit of the instant invention. In the case of the asymmetric center represented by the asterisk in Formula I, it has been found that the compound in which the 3-amino substituent is above the plane of the structure, as seen in Formula Ia, is more active and thus more preferred over the compound in which the 3-amino substituent is below the plane of the structure. In the substituent $(X)_n$, when n = 0, the asymmetric center is designated as the R-isomer. When n = 1, this center will be designated according to the R/S rules as either R or S depending upon the value of X.



Ia

The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic and the like. In addition, certain compounds containing an acidic function such as a carboxy or tetrazole, can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

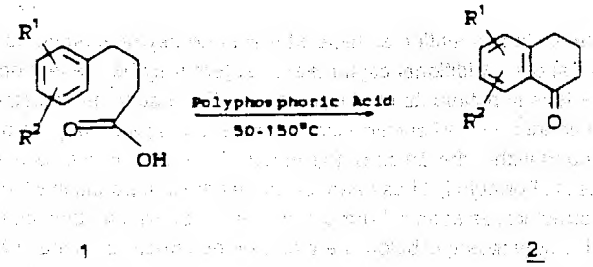
The compounds (I) of the present invention are prepared from aminolactam intermediates such as those of formula II. The preparation of these intermediates is described in the following reaction Schemes.



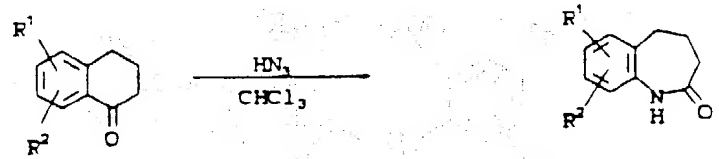
II

Benzo-fused lactams 3 wherein the lactam is a seven-membered ring are conveniently prepared from substituted tetralones 2 using known procedures. The substituted tetralones are, in some cases, commercially available or are prepared from a suitably substituted derivative of 4-phenylbutyric acid 1. Cyclization of 1 can be achieved by a number of methods well known in the literature including treatment with polyphosphoric acid at elevated temperatures as shown in Scheme 1.

Scheme 1



1 2

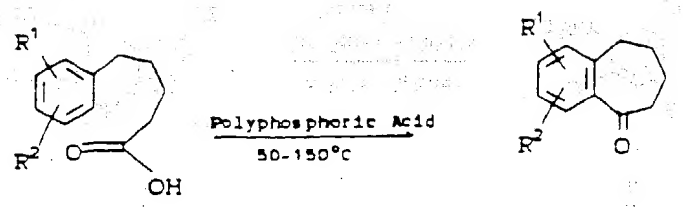


2 3

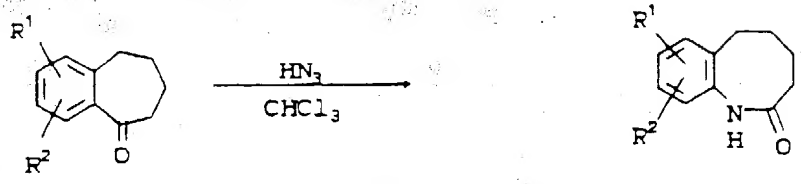
Conversion of substituted tetralones 2 to benzolactams 3 can be achieved by a number of methods familiar to those skilled in the art. A suitable method involves the use of hydrazoic acid (Schmidt reaction) to form the substituted benzolactam 3.

Benzo-fused lactams wherein the lactam is an eight-membered ring (6) are prepared as described by D. H. Jones, et al, J. Chem. Soc. C, 2176-2181 (1969) by an analogous series of transformations starting from a substituted derivative of 5-phenylpentanoic acid 4 as shown in Scheme 2.

Scheme 2



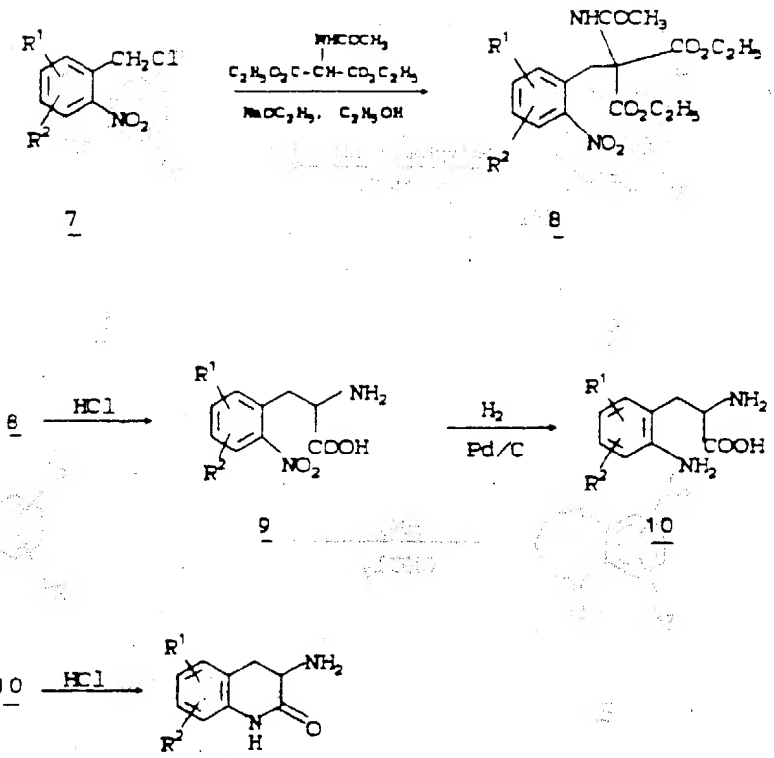
4 5



5 6

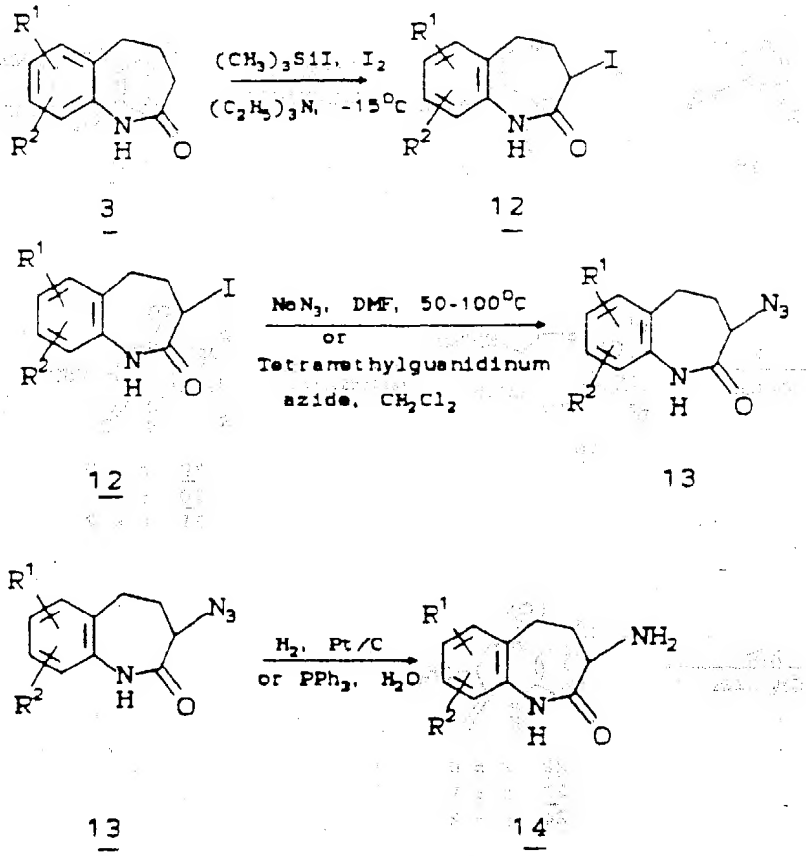
As shown in Scheme 3, 3-aminobenzolactam analogs wherein the lactam is a six-membered ring (11) are prepared from a substituted derivative of 2-nitrobenzyl chloride (or bromide) 7 by the method of A. L. Davis, et al, Arch. Biochem. Biophys, 102, 48-51 (1963) and references cited therein.

Scheme 3



Conversion of substituted benzo-fused lactams to the requisite 3-amino derivatives can be achieved by a number of methods familiar to those skilled in the art, including those described by Watthey, et al, J. Med. Chem., 28, 1511-1516 (1985) and references cited therein. One common route proceeds via the intermediacy of a 3-halo (chloro, bromo or iodo) intermediate which is subsequently displaced by a nitrogen nucleophile, typically azide. A useful method of forming the 3-iodobenzolactam intermediates 12 involves treating the benzolactam with two equivalents each of iodotrimethylsilane and iodine at low temperature, as illustrated in Scheme 4 for the seven-membered ring analogs 3.

Scheme 4



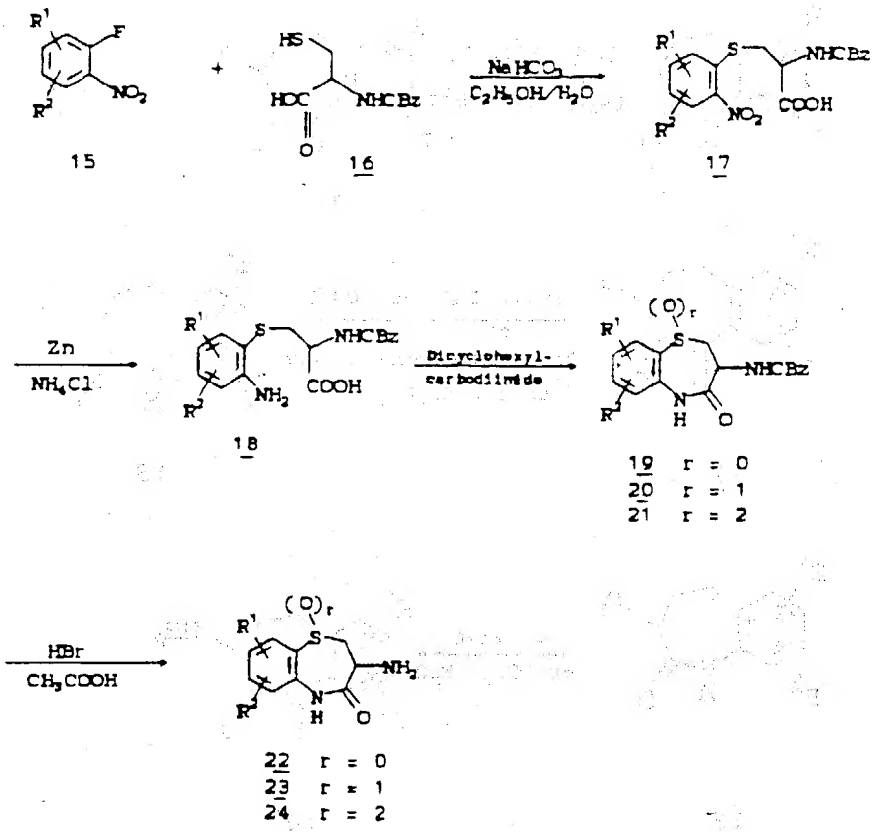
3 12 12 13 13 14

Elaboration of the iodo-benzolactams to the desired aminolactam intermediates II is achieved by a two-step procedure illustrated in Scheme 4. Typically, iodo-benzolactams 12 are treated with sodium azide in N,N-dimethylformamide at 50-100°C to give the 3-azido derivatives 13. Alternatively, tetramethylguanidinium azide in a solvent such as methylene chloride can be employed to achieve similar results. Hydrogenation with a metal catalyst, such as platinum on carbon, or alternatively, treatment with triphenylphosphine in wet toluene, results in formation of the amine derivative 14. Formation of the analogous derivatives of the eight-membered benzolactams is also achieved by the routes shown in Scheme 4.

Chiral aminobenzolactams are obtained by resolution of the racemates by classical methods familiar to those skilled in the art. For example, resolution can be achieved by formation of diastereomeric salts of the racemic amines with optically active acids such as D- and L-tartaric acid. Determination of absolute stereochemistry can be achieved in a number of ways including X-ray analysis of a suitable crystalline derivative.

Intermediates of Formula II wherein X is a sulfur atom are prepared by methods described in the literature and known to those skilled in the art. As illustrated in Scheme 5, the seven-membered ring analog 22 is prepared from a protected derivative of cysteine 16 by the method of Slade, et al, J. Med. Chem., 28, 1517-1521 (1985) and references cited therein (Cbz = benzyloxycarbonyl).

Scheme 5



15 16 17

18

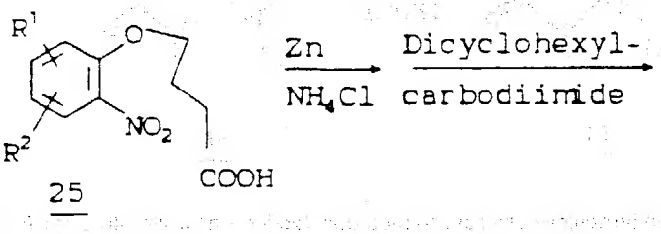
19 r = 0
20 r = 1
21 r = 2

22 r = 0
23 r = 1
24 r = 2

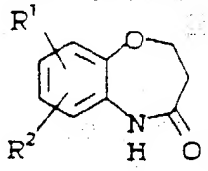
Sulfoxide and sulfone intermediates 23 and 24 are prepared by oxidation of 19 with various oxidants such as sodium periodate or meta-chloroperbenzoic acid. Eight-membered ring intermediates of Formula II wherein X is sulfur can be prepared by an analogous route starting from derivatives of homo-cysteine.

Intermediates of Formula II wherein X is an oxygen atom are prepared by methods described in the literature and known to those skilled in the art. For example, the seven-membered ring analog 26 can be prepared from a substituted derivative of 3-(2-nitrophenoxy)butyric acid 25 by the method of J. Ott, Arch. Pharm. (Weinheim, Ger.), 323(9), 601-603 (1990).

Scheme 6



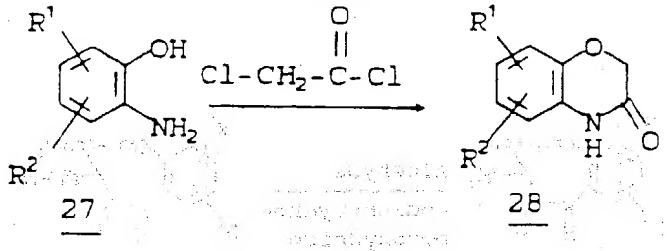
25



26

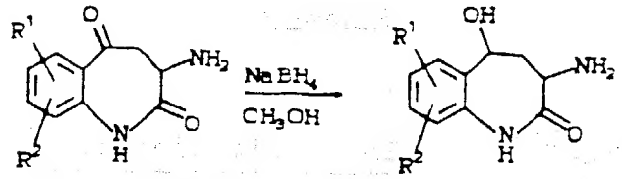
Six-membered ring analogs wherein X is oxygen (28) may be prepared by reaction of a substituted derivative of 2-aminophenol 27 with chloroacetyl chloride by the method of Huang and Chan, Synthesis, 10, 851 (1984) and references cited therein. Subsequent incorporation of an amino group at the 3 position of either 26 or 28 is achieved by the methods described in Scheme 4.

Scheme 7



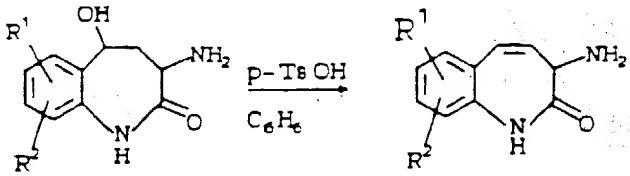
27 28

Seven-membered ring analogs of Formula II wherein X is C=O can be prepared from derivatives of tryptophan as described in the Australian Journal of Chemistry, 33, 633-640 (1980). Seven-membered ring analogs of Formula II wherein X is CH=CH can be prepared from the aforementioned analogs wherein X is C=O. Treatment of 37 with chemical reducing agents such as sodium borohydride in a polar solvent such as methanol or ethanol results in reduction to give the secondary alcohol derivative 38 (X=CHOH).



37 38

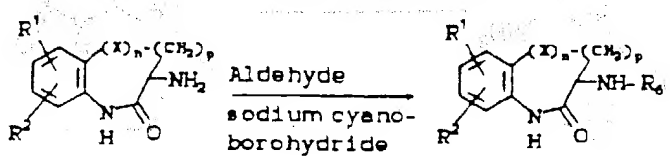
Dehydration of 38 can be achieved by several methods decribed in the literature and familiar to those skilled in the art. For example, treatment of 38 in an inert solvent, such as benzene, with a strong acid such as p-toluenesulfonic acid, will result in dehydration to the unsatured analog 39.



38 39

Intermediates of formula II can be further elaborated to new intermediates (formula III) which are substituted on the amino group (Scheme 8). Reductive alkylation of II with an aldehyde is carried out under conditions known in the art; for example, by catalytic hydrogenation with hydrogen in the presence of platinum, palladium or nickel catalysts or with chemical reducing agents such as sodium cyanoborohydride in an inert solvent such as methanol or ethanol.

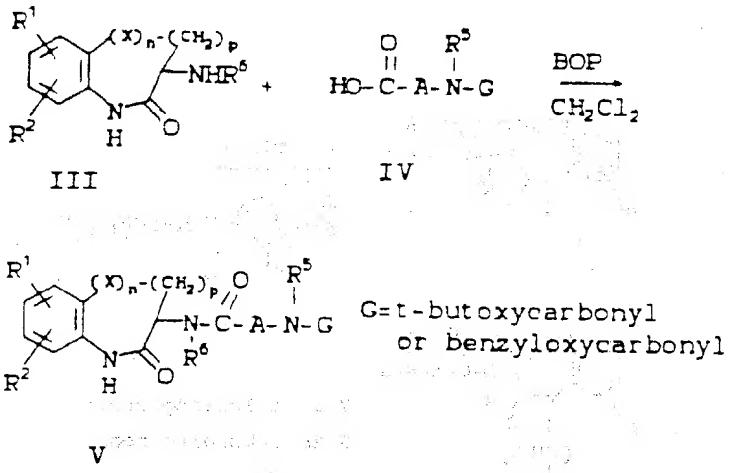
Scheme 8



II III

Attachment of the amino acid sidechain to intermediates of formula III is accomplished by the route shown in Scheme 9. Coupling is conveniently carried out by the use of an appropriately protected amino acid derivative, such as that illustrated by formula IV, and a coupling reagent such as benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate ("BOP") in an inert solvent such as methylene chloride. Separation of unwanted side products, and purification of intermediates is achieved by chromatography on silica gel, employing flash chromatography (W.C. Still, M. Kahn and A. Mitra, J. Org. Chem., 43, 2923 (1978)) or by medium pressure liquid chromatography.

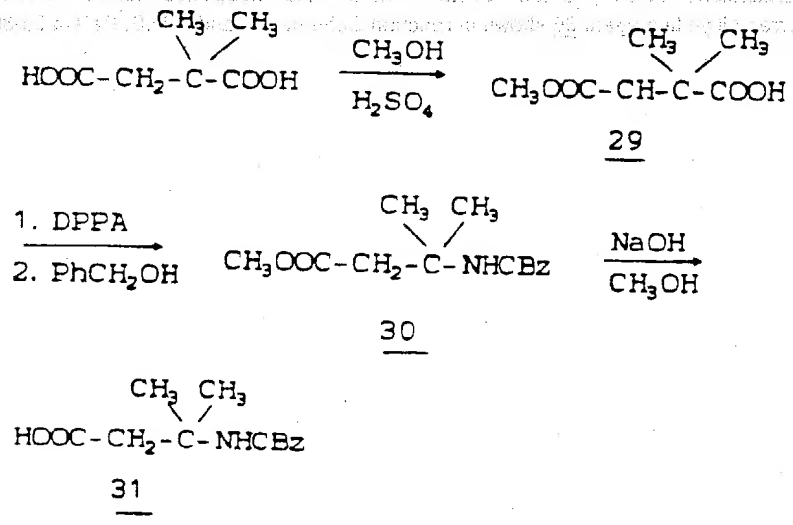
Scheme 9



III IV V

The protected amino acid derivatives IV are, in many cases, commercially available in t-butoxycarbonyl (BOC) or benzyloxycarbonyl (CBz) forms. A useful method to prepare the preferred sidechain 31 is shown in Scheme 10.

Scheme 10



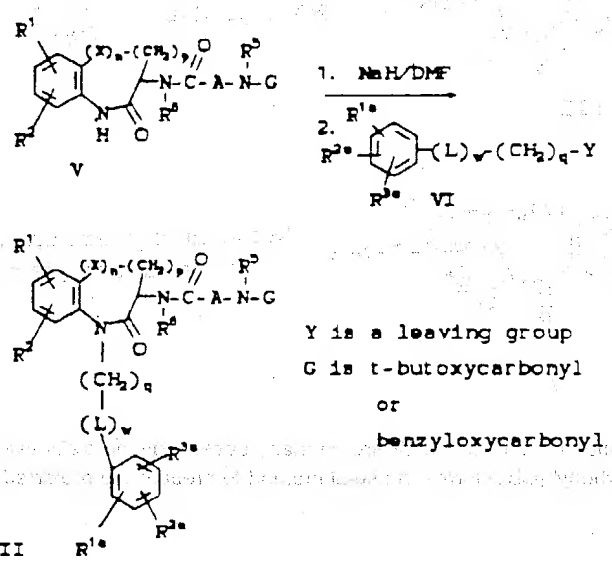
29 30 31

Formation of the monomethyl ester 29 of 2,2-dimethylsuccinic acid is achieved by treatment of a methanolic solution with a catalytic amount of a strong acid, such as sulfuric acid. Treatment of 29 with diphenylphosphoryl azide (DPPA) followed by benzyl alcohol results in formation of the benzyloxycarbonyl (CBz) compound 30. Alkaline hydrolysis with sodium hydroxide in methanol affords the product 31.

Intermediates of formula VII can be prepared as shown in Scheme 11 by treatment of the desired lactam intermediate V with an alkylating agent VI, wherein L is a good leaving group such as Cl, Br, I, O-methanesulfonyl or O-(p-toluenesulfonyl). Alkylation of intermediates of formula V is conveniently carried out in anhydrous dimethyl formamide (DMF) in the presence of bases such as sodium hydride or potassium t-butoxide for a period of 0.5 to 24 hours at temperatures of 20-100°C. Substituents on the alkylating agent VI may need to be protected during alkylation. A description of such protecting groups may be found in: Protective Groups in Organic Syn-

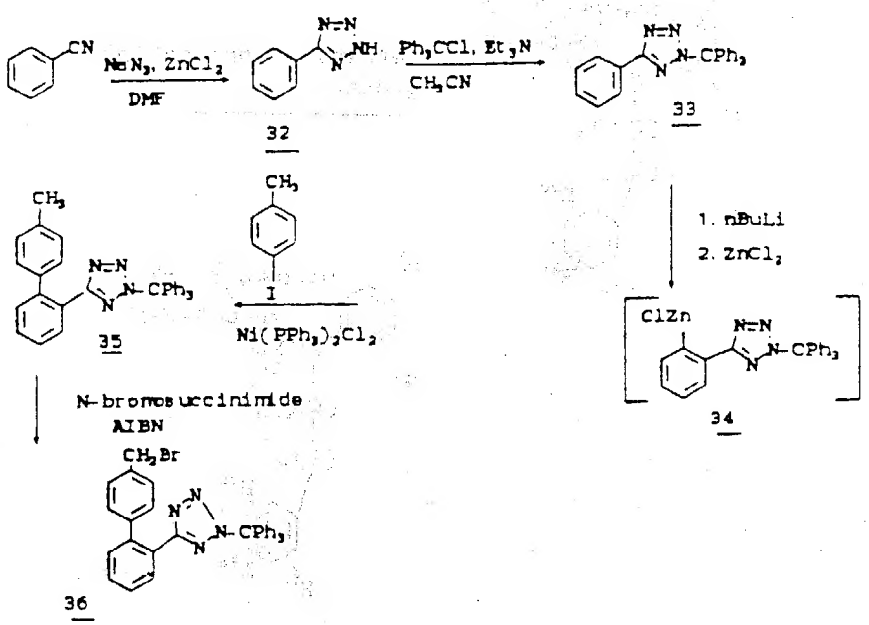
thesis, T.W. Greene, John Wiley and Sons, New york, 1981.

Scheme 11



Alkylating agents VI are, in some cases commercially available compounds or may be prepared as described in EPO publications 253,310; 291,969; 324,377 and the references cited therein. A useful method to prepare the preferred alkylating agent 36 shown in reaction Scheme 12, and in U.S. Patent 5,039,814.

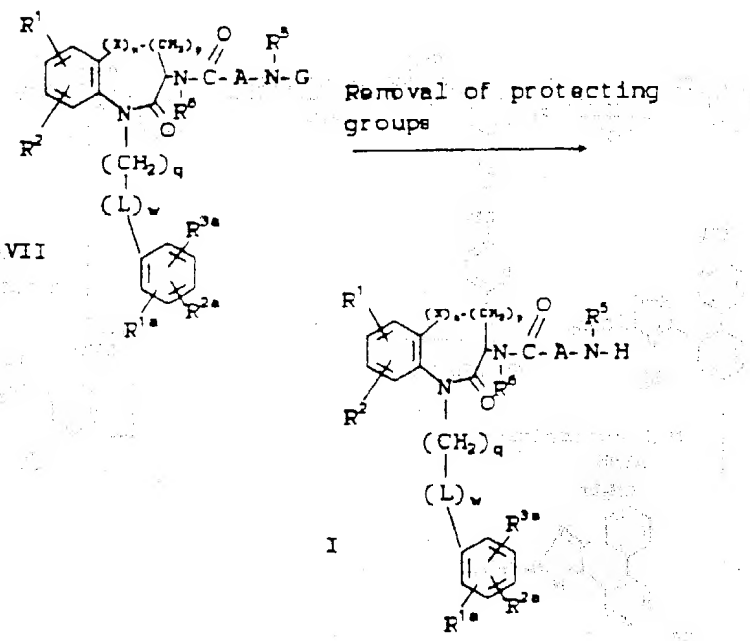
Scheme 12



As outlined in Scheme 12, benzonitrile is treated with sodium azide and zinc chloride to give 5-phenyltetrazole 32 which is converted to the N-trityl derivative 33 by treatment with triphenylmethyl chloride and triethylamine. The zinc reagent 34 was prepared by treatment with n-butyl lithium followed by zinc chloride. Coupling with 4-iodotoluene using the catalyst bis(triphenylphosphine)-nickel(II) dichloride gives the biphenyl product 35 in high yield. Reaction with N-bromosuccinimide and AIBN gives bromide 36.

Conversion to the final products of formula I wherein R^4 is hydrogen, is carried out by simultaneous or sequential removal of all protecting groups from intermediate VII as illustrated in Scheme 13. Removal of benzyloxycarbonyl groups can be achieved by a number of methods known in the art; for example, catalytic hydrogenation with hydrogen in the presence of a platinum or palladium catalyst in a protic solvent such as methanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of benzyloxycarbonyl groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid. Catalytic hydrogenation is also employed in the removal of N-triphenylmethyl (trityl) protecting groups. Removal of t-bytoxycarbonyl (BOC) protecting groups is carried out by treatment of a solution in a solvent such as methylene chloride or methanol, with a strong acid, such as hydrochloric acid or trifluoroacetic acid. Conditions required to remove other protecting groups which may be present can be found in Protective Groups in Organic Synthesis.

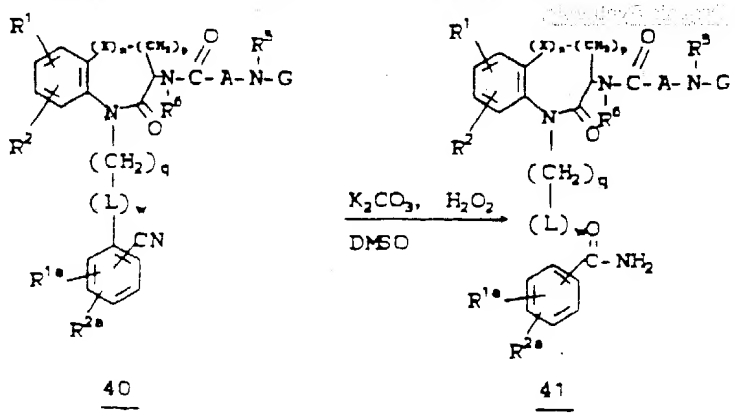
Scheme 13



Compounds of formula I wherein R^4 and R^5 are each hydrogen can be further elaborated by reductive alkylation with an aldehyde by the aforementioned procedures or by alkylations such as by reaction with various epoxides. The products, obtained as hydrochloride or trifluoroacetate salts, are conveniently purified by reverse phase high performance liquid chromatography (HPLC) or by recrystallization.

Compounds of Formula I wherein R^{3a} or R^{3b} are taken as $R^4R^5NCO(CH_2)_v$ and v is 0 can be prepared by several methods. For example, as shown in Scheme 14, compound 41 wherein R^4 and R^5 are both hydrogen is conveniently prepared by hydrolysis of a nitrile precursor 40.

Scheme 14

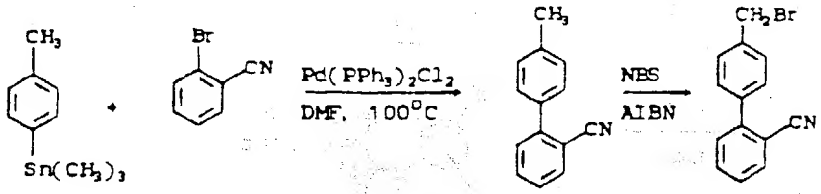


40 41

Thus, treatment of the nitrile 40 with hydrogen peroxide and a strong base, such as potassium carbonate, in a polar solvent, such as dimethylsulfoxide at temperatures of 25°C to 150°C results in formation of the amide derivative 41. The precursor 40 can be prepared from an appropriate alkylating agent VI, where R^{3a} is cyano, as described in Scheme 11.

A useful method of preparing the alkylating agent 44 is outlined in Scheme 15.

Scheme 15

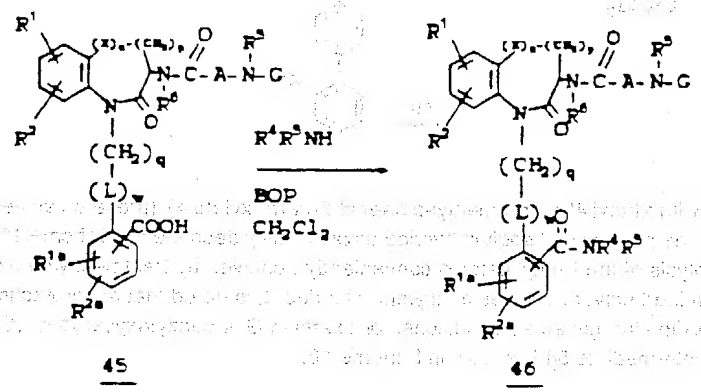


42 43 44

Thus, treatment of 4-(methylphenyl)trimethyl stannane 42 with 2-bromobenzonitrile in dimethylformamide at 100°C in the presence of bis-triphenylphosphine palladium (II) chloride results in coupling to form the biphenyl nitrile 43 in high yield. Conversion to bromide 44 is achieved by treatment with N-bromosuccinimide and a radical initiator, such as azobisisobutyronitrile (AIBN), in refluxing carbon tetrachloride.

Compounds of Formula I wherein R^{3a} or R^{3b} are taken as $R^4R^5NCO(CH_2)_v$ and v is O and R^4 and/or R^5 are not hydrogen are prepared from the corresponding carboxylic acid derivatives 45 as shown in Scheme 16.

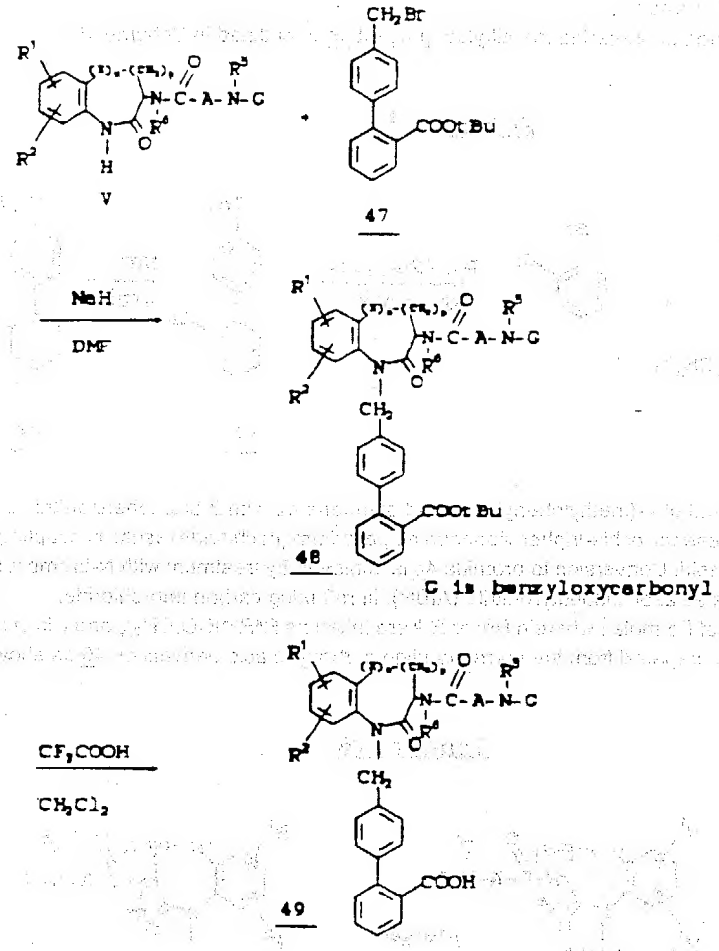
Scheme 16



45 46

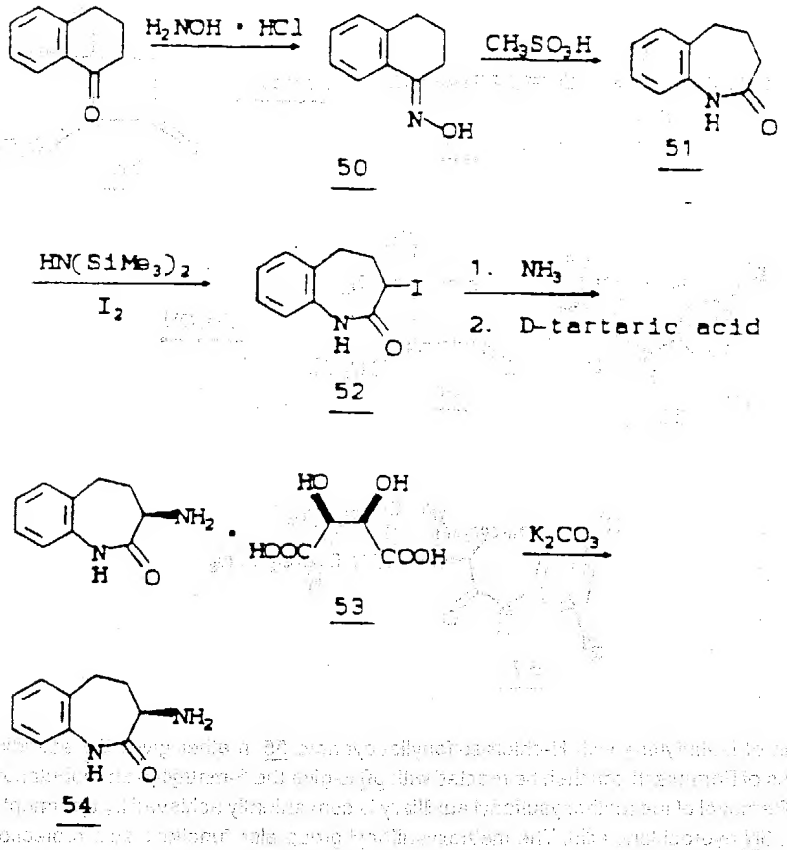
Coupling of the carboxylic acid derivative 45 with R^4R^5NH is conveniently carried out by the use of a coupling reagent such as benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate ("BOP") in an inert solvent such as methylene chloride. The requisite carboxylic acid precursors can be prepared as illustrated in Scheme 17 for the biphenyl compound 49.

Scheme 17



Alkylation of V with t-butyl 4'-bromomethyl-biphenyl-2-carboxylate 47 (prepared as described in EPO Publication 324,377) in the presence of sodium hydride as previously described in Scheme 11 gives the adduct 48 in high yield. Hydrolysis of the t-butyl ester is conveniently achieved by treatment with a strong acid, such as trifluoroacetic, in an inert solvent such as methylene chloride. It is noted that the protecting group G in this instance must be inert to strongly acidic conditions, for example G is benzyloxycarbonyl (CBz). A useful preparation of the chiral intermediate 54 is shown in Scheme 18.

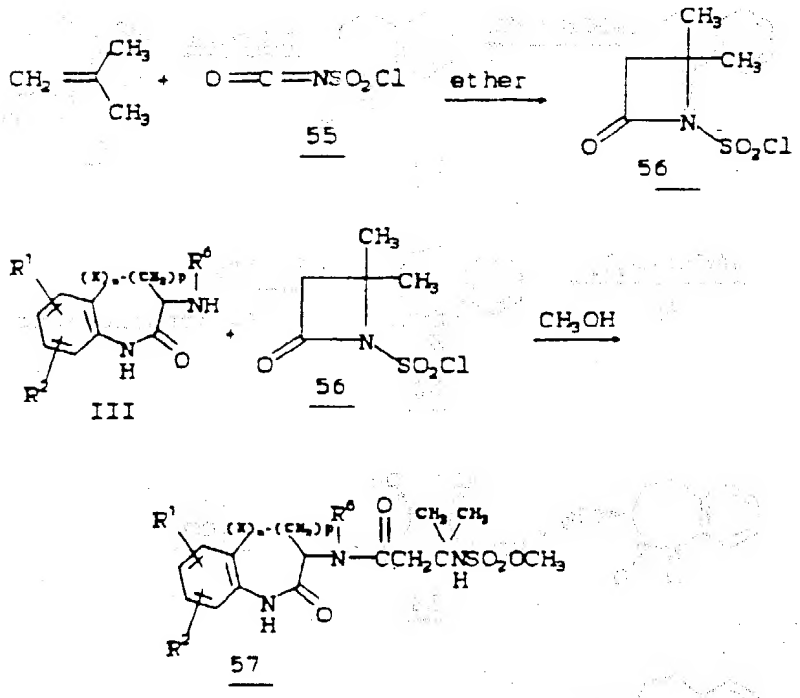
Scheme 18



Conversion of 1-tetralone to the seven-membered benzolactam 51 is achieved by Beckman rearrangement of the intermediate oxime 50. Treatment of 51 with iodine and hexamethyldisilazane gives the 3-iodo derivative 52 which is sequentially treated with ammonia and D-tartaric acid to give the diastereomeric D-tartrate salt 53 after recrystallization. Liberation of the free amine 54 is achieved by neutralization of the D-tartrate salt with potassium carbonate followed by extractive isolation.

An improved route to compounds containing the 3-amino-3-methylbutanamide sidechain is presented in Scheme 19.

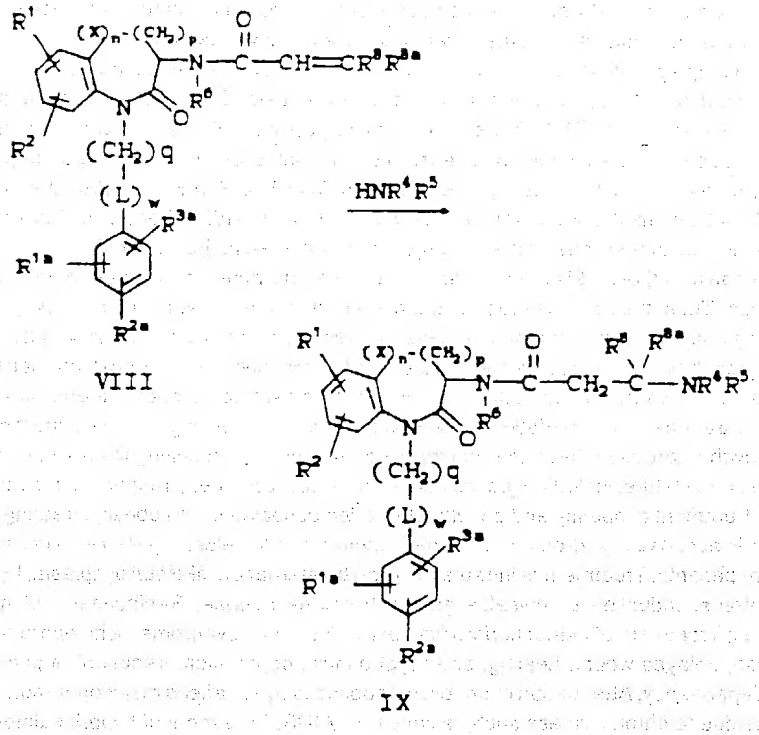
Scheme 19



Reaction of isobutylene with N-chlorosulfonylisocyanate 55 in ether gives the azetidinone derivative 56. Intermediates of Formula III can then be reacted with 56 to give the 3-methyl-3-aminobutanamide intermediates 57 directly. Removal of the methoxysulfonyl auxilliary is conveniently achieved by treatment with aqueous acid, for example, 6N hydrochloric acid. The methoxysulfonyl group also functions as a protection group G which is inert to the basic conditions employed in the subsequent alkylation step as illustrated in Scheme 11.

An alternate route to the sub-class of compounds of Formula I that can be described by Formula IX is show in Scheme 20.

Scheme 20



VIII

IX

Thus, reaction of intermediates of Formula VIII with HNR^4R^5 neat or in a polar solvent such as dimethylsulfoxide at temperatures of 50°C to 200°C, results in a Michael addition to give compounds of Formula IX. Compounds of Formula VIII may themselves be prepared by the transformations illustrated in Schemes 9 and 11.

It is noted that the order of carrying out the foregoing reaction schemes is not significant and it is within the skill of one skilled in the art to vary the order of reactions to facilitate the reaction or to avoid unwanted reaction products.

The growth hormone releasing compounds of Formula I are useful in vitro as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits growth hormone release. Other hormones that are important and in need of study as to their effect on growth hormone release include the gonadal hormones, e.g., testosterone, estradiol, and progesterone; the adrenal hormones, e.g., cortisol and other corticoids, epinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive intestinal peptides, e.g., bombesin; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The compounds of Formula I can also be employed to nvestigate the possible negative or positive feedback effects of some of the pituitary hormones, e.g., growth hormone and endorphin peptides, on the pituitary to modify growth hormone release. Of particular scientific importance is the use of these compounds to elucidate the subcellular mechanisms mediating the release of growth hormone.

The compounds of Formula I can be administered to animals, including man, to release growth hormone in vivo. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, and to increase milk production in such animals. In addition, these compounds can be administered to humans in vivo as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula I can be administered in vivo to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly determining the ability of the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise a growth promoting agent in addition to at least one of the compounds of Formula I or another composition which exhibits a different activity, e.g., an antibiotic or other pharmaceutically active material.

Growth promoting agents include, but are not limited to, TRH, diethylstilbesterol, theophylline, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

A still further use of the disclosed novel benzo-fused lactam growth hormone secretagogues is in combination with other growth hormone secretagogues such as GHRP-6, GHRP-1 as described in U.S. Patent Nos. 4,411,890; and publications WO 89/07110 and WO 89/07111 and B-HT920 or growth hormone releasing factor and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2.

As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses of growth hormone may be summarized as follows: stimulating growth hormone release in elderly humans; Prevention of catabolic side effects of glucocorticoids, treatment of osteoporosis, stimulation of the immune system, treatment of retardation, acceleration of wound healing, accelerating bone fracture repair, treatment of growth retardation, treating renal failure or insufficiency resulting in growth retardation, treatment of physiological short stature, including growth hormone deficient children, treating short stature associated with chronic illness, treatment of obesity and growth retardation associated with obesity, treating growth retardation associated with Prader-Willi syndrome and Turner's syndrome; Accelerating the recovery and reducing hospitalization of burn patients; Treatment of intrauterine growth retardation, skeletal dysplasia, hypercortisolism and Cushings syndrome; Induction of pulsatile growth hormone release; Replacement of growth hormone in stressed patients; Treatment of osteochondrodysplasias, Noonans syndrome, schizophrenia, depression, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treatment of pulmonary dysfunction and ventilator dependency; Attenuation of protein catabolic response after a major operation; reducing cachexia and protein loss due to chronic illness such as cancer or AIDS. Treatment of hyperinsulinemia including nesidioblastosis; Adjuvant treatment for ovulation induction; To stimulate thymic development and prevent the age-related decline of thymic function; Treatment of immunosuppressed patients; Improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; Stimulation of osteoblasts, bone remodelling, and cartilage growth; Stimulation of the immune system in companion animals and treatment of disorders of aging in companion animals; Growth promotant in livestock; and stimulation of wool growth in sheep.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, , sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known

in the art.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 100 mg/kg. of body weight daily are administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

Example 1

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 3-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

A solution of 9.22 g (45.6 mmol) of 3-azido-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (prepared by the method of Watthey, et al., J. Med. Chem., 28, 1511-1516 (1985)) in 30mL methanol was hydrogenated at 40psi in the presence of 1.0g of 5% Pt/C for 4.5 hours. Celite was added and the mixture filtered through a pad of Celite. The filtrate was concentrated and allowed to stand for 16 hours at room temperature which resulted in formation of crystals. The material was isolated by filtration and dried under vacuum to afford 4.18g (23.7mmol, 52%) of the product. The mother liquors were diluted to 100mL with methanol, treated with 2g of charcoal, filtered through Celite and the filtrate concentrated under vacuum to approximately 15 mL. A second crop formed yielding 2.02 g of product (11.5mmol, 25%). Another recycling of the mother liquors afforded a third crop of 0.88g (5.0, 11%). A total of 7.08g (40.2mmol, 88%) of the product was thus obtained. ^{1}H NMR (200MHz,$CDCl_3$): 1.6 (br s,2H), 1.80 (m,1H), 2.55 (m,2H), 2.88 (m,1H), 3.42 (dd;7Hz,11Hz;1H), 6.98 (d,8Hz,1H), 7.2 (m,3H), 8.3 (br s,1H). FAB-MS: calculated for $C_{10}H_{12}N_2O$ 176; found 177 (M+H,100%).

Step B: 3(R)-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

2.37g (13.5mmol) of 3-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Step A) and 2.02g (13.5mmol) of L-tartaric acid were suspended in 40mL of ethanol. The mixture was gently heated and complete dissolution achieved by dropwise addition of 5mL of distilled water. The solution was cooled to room temperature and aged overnight. The solid that formed was removed by filtration, washed with ethanol/diethyl ether (1:1) and dried under vacuum to afford 1.75g of crude L-tartrate salt. The mother liquors were evaporated to dryness under vacuum, redissolved in 40mL of water and the pH adjusted to 10-11 by the addition of solid potassium carbonate. The mixture was extracted with chloroform (6x20mL) and the combined extracts washed with water (1x) and brine (1x), dried over potassium carbonate, filtered and solvents removed under vacuum to afford 1.29g (7.33mmol) of partially enriched 3(R) amine.

The original 1.75g batch of L-tartrate salt was recrystallized twice from aqueous ethanol to afford 1.03g (3.17mmol,24%) of purified L-tartrate salt with $[a]_D=^-212°$ (c=1, H_2O). The purified L-tartrate salt was dissolved in 20mL of water and the pH adjusted to 10-11 by the addition of solid potassium carbonate. The mixture was extracted with chloroform (5x10mL); combined extracts were washed with water and brine then dried over potassium carbonate, filtered and solvents removed under vacuum to afford 522mg (2.96mmol,22% overall) of the 3(S) amine, $[a]_D=^-446°$ (c=1,CH_3OH).

The remaining 1.29g (7.33mmol) of partially enriched 3(R) amine was treated with 1.10g (7.33mmol) of D-tartaric acid as described above and the resulting salt recrystallized twice from aqueous ethanol to afford 1.20g of purified D-tartrate salt, $[a]_D=^-214°$ (c=1,H_2O). The purified D-tartrate salt was dissolved in 20mL of water and the free base isolated as described above to give 629mg (3.57mmol,26% overall) of the 3(R) amine, $[a]_D=^+455°$ (c=1,CH_3OH).

Step C: 2,2-Dimethylbutanedioic acid, 4-methyl ester

2,2-dimethylsuccinic acid (20g, 137mmol) dissolved in 200mL absolute methanol at 0° was treated dropwise with 2mL concentrated sulfuric acid. After the addition was complete, the mixture was allowed to warm to room temperature and stirred for 16 hours.

The mixture was concentrated in vacuo to 50mL and slowly treated with 200mL of saturated aqueous sodium bicarbonate. The mixture was washed with hexane (3x) and the aqueous layer removed and cooled in

an ice bath. The mixture was acidified to pH 2 by slow addition of 6N HCl then extracted with ether (8x). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and solvents removed in vacuo. The residue was dried at room temperature under vacuum to afford 14.7g (91.8mmol, 67%) of a viscous oil that slowly solidified upon standing. ^{1}H NMR analysis indicates the product is a mixture of the title compound and 15% of the isomeric 2,2-dimethylbutanedioic acid, 1-methyl ester. NMR (200MHz, $CDCl_3$) of title compound: 1.29 (s,6H), 2.60 (s,2H), 3.66 (s,3H). NMR (200MHz, $CDCl_3$) of isomer: 1.28 (s,6H), 2.63 (s,2H), 3.68 (s,3H).

Step D: 3-[Benzyloxycarbonylamino]-3-methylbutanoic acid, methyl ester

To 14.7g (91.8mmol) of 2,2-dimethylbutanedioic acid-4-methyl ester (Step C), containing 15% of the isomeric 1-methyl ester compound, in 150mL benzene was added 13mL of triethylamine (9.4g, 93mmol, 1.01eq) followed by 21.8mL diphenylphosphoryl azide (27.8g, 101mmol, 1.1eq). The mixture was heated under nitrogen at reflux for 45 minutes then 19mL (19.9g, 184mmol, 2eq) of benzyl alcohol was added and refluxing continued for 16 hours.

The mixture was cooled, filtered and the filtrate concentrated to a minimum volume under vacuum. The residue was redissolved in 250mL ethyl acetate, washed with water (1x), saturated aqueous sodium bicarbonate (2x) and brine (1x). The organic layer was removed, dried over magnesium sulfate, filtered and the filtrate concentrated to a minimum volume in vacuo. The crude product was purified by medium pressure liquid chromatography on silica, eluting with hexane/ethyl acetate (4:1), to afford 18.27g (68.9mmol, 75%) of the title compound as a pale yellow liquid in addition to a small amount of pure 3-[benzyloxycarbonylamino]-2,2-dimethylpropanoic acid, methyl ester. ^{1}H NMR (200MHz, $CDCl_3$) of title compound: 1.40 (s,6H), 2.69 (s,2H), 3.63 (s,3H), 5.05 (s,2H), 5.22 (br s,1H), 7.32 (s,5H). ^{1}H NMR (200MHz, $CDCl_3$) of 3-[benzyloxycarbonylamino]-2,2-dimethylpropanoic acid, methyl ester (200MHz, $CDCl_3$): 1.19 (s,6H), 3.30 (d,7Hz,2H; resonance collapses to singlet in CD_3OD), 3.67 (s,3H), 5.09 (s,2H), 5.22 (br s,1H; resonance not observed in CD_3OD), 7.3 (br s,5H).

Step E: 3-Benzyloxycarbonylamino-3-methylbutanoic acid

A solution of 18.27g (68.9mmol) of methyl 3-benzyloxycarbonylamino-3-methylbutanoate (Step D) in 20mL of methanol at room temperature was treated dropwise with 51mL of 2N NaOH (102mmol, 1.5eq). The mixture was stirred at room temperature for 16 hours then transferred to a separatory funnel and washed with hexane (3x). The aqueous layer was removed, cooled to 0° and slowly acidified to pH 2 (paper) by dropwise addition of 6N HCl. This mixture was extracted with ether (6x); combined extracts were washed with 1N HCl and brine, then dried over magnesium sulfate, filtered and solvent removed under vacuum to afford 17.26g (68.7mmol, 99%) of the product. ^{1}H NMR (200MHz,$CDCl_3$): 1.42 (s,6H), 2.77 (s,2H), 5.06 (s,2H), 5.2 (br s,1H), 7.3 (s,5H).

Step F: 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butamide

To a solution of 252mg (1.43mmol) of 3(R)-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Step B) in 4mL of methylene chloride at room temperature was added 400mg (1.60mmol, 1.1eq) of 3-benzyloxycarbonylamino-3-methylbutanoic acid (Step E) followed by 760mg (1.7mmol, 1.2eq) benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate and 0.50mL of diisopropylethylamine (380mg, 2.9mmol, 2eq). After 3 hours at room temperature, the mixture was diluted into 30mL of ethyl acetate and washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate (2x) and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate to afford 586mg (1.43mmol, 100%) of the product. ^{1}H NMR (200MHz,$CDCl_3$): 1.38 (s,3H), 1.39 (s,3H), 1.82 (m,1H), 2.52 (s,2H), 2.5-3.0 (m,3H), 4.51 (m,1H), 5.07 (br s,2H), 5.57 (br s,1H), 6.68 (d,7Hz,1H), 6.97 (d,8Hz,1H), 7.1-7.4 (m,8H), 7.61 (br s,1H). FAB-MS: calculated for $C_{23}H_{27}N_3O_4$ 409; found 410 (M+H,100%); $[a]_D$=+137° (c=1, $CHCl_3$).

Step G: 5-Phenyltetrazole

Zinc chloride (3.3g, 24.3mmol, 0.5eq) was added to 15mL of N,N-dimethylformamide in small portions while maintaining the temperature below 60°C. The suspension of zinc chloride was cooled to room temperature and treated with 5.0g of benzonitrile (48.5mmol, 1.0eq) followed by 3.2g of sodium azide (48.5mmol, 1.0eq). The heterogeneous mixture was heated at 115°C with agitation for 18 hours. The mixture was cooled to room temperature, water (30mL) was added and the mixture acidified by the addition of 5.1mL of concentrated hydro-

chloric acid. The mixture was cooled to 0°C and aged for one hour, then filtered and the filter cake washed with 15mL of cold 0.1N HCl then dried at 60°C under vacuum to afford 6.38g (43.7mmol, 90%) of the product.

Step H: 5-Phenyl-2-trityltetrazole

To a suspension of 5.0g (34.2mmol) of 5-phenyltetrazole in 55mL of acetone was added 5.0mL of triethylamine (3.6g, 35.6mmol, 1.04eq). After 15 minutes, a solution of 10.0g of triphenylmethyl chloride (35.9mmol, 1.05eq) in 20mL of tetrahydrofuran was added and the mixture stirred at room temperature for one hour. Water (75mL) was slowly added and the mixture stirred for one hour at room temperature. The product was collected by filtration, washed with 75mL of water and dried at 60°C under vacuum to give 13.3g (34.2mmol, 100%) of the product.

Step I: N-Triphenylmethyl-5-[2-(4'-methylbiphen-4-yl)] tetrazole

A solution of zinc chloride (6.3g, 46.2mmol, 0.6eq) in 35mL of tetrahydrofuran was dried over molecular sieves. 5-Phenyl-2-trityltetrazole (30.0g, 77.3mmol, 1.0eq) was dissolved in 300mL of dry tetrahydrofuran and the solution gently stirred while being degassed three times by alternating vacuum and nitrogen purges. The stirred solution was cooled to -15°C and treated slowly with 50.5mL of 1.6M n-butyllithium in hexane (80.0mmol, 1.05eq) so as to maintain the temperature below -5°C. The solution was maintained at -5 to -15°C for 1.5 hours then treated with the dried zinc chloride solution and allowed to warm to room temperature.

In a separate flask, 4-iodotoluene (20.17g, 92.5mmol, 1.2eq) and bis-(triphenylphosphine)nickel-(II) dichloride (1.5g, 2.3mmol, 0.03eq) were dissolved in 60mL of tetrahydrofuran, then degassed and left under an atmosphere of nitrogen. The mixture was cooled to 5°C and treated with 1.5mL of 3.0M solution of methylmagnesium chloride in tetrahydrofuran (4.5mmol, 0.06eq) so as to keep the temperature below 10°C. The solution was warmed to room temperature and added, under nitrogen purge, to the arylzinc solution. The reaction mixture was stirred vigorously for 8 hours at room temperature then quenched by the slow addition of a solution of 10mL of glacial acetic acid (1.6mmol, 0.02eq) in 60mL of tetrahydrofuran at a rate so that the temperature was maintained below 40°C. The mixture was stirred for 30 minutes and 150mL of 80% saturated aqueous sodium chloride was added; the reaction mixture was extracted for 30 minutes and the layers allowed to separate. The organic layer was removed and washed with 150mL of 80% saturated aqueous sodium chloride buffered to pH>10 by the addition of ammonium hydroxide. The organic phase was removed and concentrated under vacuum to approximately 50mL then 250mL of acetonitrile was added. The mixture was again concentrated under vacuum to 50mL and acetonitrile added to make the final volume 150mL. The resulting slurry was cooled at 5°C for 1 hour then filtered and washed with 50mL of cold acetonitrile followed by 150mL of distilled water. The filter cake was air dried to a free flowing solid then further dried under vacuum at 50°C for 12 hours to afford 30.0g (62.8mmol, 81%) of the product. ^{1}H NMR (200MHz, $CDCl_3$): 2.28 (s,3H), 6.9-7.05 (m,10H), 7.2-7.5 (m,12H), 7.9 (m,1H).

Step J: N-Triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole

A solution of 3.15g (6.6mmol) of N-triphenylmethyl-5-[2-(4'-methylbiphen-4-yl)] tetrazole (Step I) in 25mL of methylene chloride was treated with 1.29g (7.25mmol, 1.1eq) of N-bromosuccinimide, 80mg (0.5mmol, 0.07eq) of AIBN, 200mg of sodium acetate and 200mg of acetic acid. The mixture was heated at reflux for 2 to 16 hours then cooled and washed with saturated aqueous sodium bicarbonate. The organic layer was removed, dried over sodium sulfate, filtered and concentrated to a minimum volume by atmospheric distillation. Methyl t-butyl ether was added and distillation continued until almost all the methylene chloride was removed the the total volume reduce to approximately 12mL and 12mL of hexanes was then added. The mixture was kept at room temperature for 2 hours and the product isolated by filtration, washed with hexanes then dried under vacuum at 50°C to give 2.81g (5.04mmol, 76%) of the product. ^{1}H NMR (200MHz, $CDCl_3$): 4.38 (s,2H), 6.9-8.0 (m,23H). NMR indicates presence of approximately 1% of the starting material and 7% of the dibromo derivative.

Step K: 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]-butanamide

To a solution of 437mg (1.07mmol) of the intermediate obtained in Step F in 2mL of dry dimethylformamide at room temperature under nitrogen was added 55mg of 60% sodium hydride oil dispersion (33mg NaH, 1.38mmol, 1.3eq). After 15 minutes, a solution of 715mg (1.28mmol, 1.2eq) N-triphenyl-methyl-5-[2-(4'-bro-

momethylbiphen-4-yl)] tetrazole (Step J) in 1.5mL of dry dimethylformamide was added and the mixture stirred for 90 minutes.

The reaction mixture was added to 100mL of ethyl acetate and washed with water (2x) and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed under vacuum. Purification by medium pressure liquid chromatography on silica, eluting with ethyl acetate/hexane (1:1), afforded 902mg (1.02mmol, 95%) of the product. ^{1}H NMR (200MHz,$CDCl_3$): 1.38 (s,3H), 1.39 (s,3H), 1.68 (m,1H), 2.2-2.5 (m,5H), 4.44 (m,1H), 4.67 (d,14Hz,1H), 5.06 (s,2H), 5.12 (d,14Hz,1H), 5.63 (br 1,1H), 6.65 (d,8Hz,1H), 6.9-7.5 (m,31H), 7.85 (m,1H).

Step L: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

A solution of 902mg (1.02mmol) of the intermediate obtained in Step H in 5mL methanol was hydrogenated at room temperature and one atmosphere over 160mg of 20% $Pd(OH)_2$/C for 14 hours. The mixture was filtered through Celite and concentrated under vacuum. The residue was purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 80% methanol over 10 minutes) to afford 568mg (0.91mmol, 89%) of the title compound. ^{1}H NMR (200MHz,CD_3OD): 1.33 (s,3H), 1.37 (s,3H), 2.0-2.6 (m,6H), 4.35 (dd;7,11Hz;1H), 4.86 (d,15Hz,1H), 5.20 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.15-7.35 (m,6H), 7.45-7.70 (m,4H). FAB-MS: calculated for $C_{29}H_{31}N_7O_2$ 509; found 510 (M+H,100%).

Example 2

3-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-propanamide, mono(hydrochloride)

Step A 3-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-propanamide

To a solution of 50mg (0.28mmol) 3-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1, Step A) in 2mL methylene chloride at room temperature was added 56mg (0.30mmol, 1.05eq) 3-(t-butoxycarbonylamino)propanoic acid followed by 0.1mL diisopropylethylamine (74mg, 0.57mmol, 2eq) and 190mg (0.43mmol, 1.5eq) benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate. After 1 hour at room temperature, the mixture was added to 20mL ethyl acetate and washed with 1M aqueous citric acid, saturated aqueous sodium bicarbonate and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed in vacuo. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate/hexane (2:1) to afford 76mg (0.22mmol, 77%) of product as a white solid. ^{1}H NMR (200MHz, $CDCl_3$): 1.40 (s,9H), 1.95 (m,1H), 2.40 (t,6Hz,2H), 2.6-3.0 (m,3H), 3.36 (q,6Hz,2H), 4.52 (m,1H), 5.15 (br t,1H), 6.58 (br d,1H), 7.0-7.3 (m,4H), 7.6 (br s,1H). FAB-MS: calc. for $C_{18}H_{25}N_3O_4$ 347; found 348 (M+H,35%).

Step B 3-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide

To a solution of 68mg (0.2mmol) of the intermediate obtained in Step A in 0.5mL dry dimethylformamide under nitrogen was added 10mg of 60% sodium hydride oil dispersion (6mg NaH, 0.25mmol, 1.3eq). After 15min., a solution of 142mg (0.26mmol, 1.3eq) N-triphenylmethyl-5-(4'-bromomethylbiphen-2-yl)tetrazole (Example 1, Step J) in 0.5mL dimethylformamide was added and the mixture stirred at room temperature for 4 hours. The mixture was added to 30mL ethyl acetate and washed twice with pH 7.0 phosphate buffer and once with brine. The organic layer was removed, dried over magnesium sulfate filtered and solvents removed in vacuo. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate to afford 152mg (0.18mmol, 94%) of the product as a white foam. ^{1}H NMR (200MHz, $CDCl_3$): 1.40 (s,9H), 1.77 (m,1H), 2.3-2.6 (m,5H), 3.35 (q,6Hz,2H), 4.45 (m,1H), 4.70 (d,15Hz,1H), 5.12 (d,15Hz,1H), 6.53 (d,7Hz,1H), 6.9-7.5 (m, approx. 25H), 7.85 (m,1H).

Step C 3-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-propanamide

The intermediate obtained in Step B (150mg, 0.18mmol) dissolved in 5mL methanol was hydrogenated over

30mg of $Pd(OH)_2$ on carbon at one atmosphere for 2 hours. The mixture was filtered through Celite and the filtrate concentrated under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate/acetonitrile/ methanol (9:1:1) to afford 62mg (0.11mmol, 59%) of the product as a colorless glass. ^1H NMR (200MHz, CD_3OD): 1.39 (s,9H), 2.0-2.5 (m,6H), 3.26 (t,7Hz,2H), 4.31 (dd;7,12Hz;1H), 4.83 (d,16Hz,1H), 5.20 (d,16Hz,1H), 6.98 (d,8Hz,2H), 7.1-7.6 (m,10H). FAB-MS: calc. for $C_{32}H_{35}N_7O_4$ 581; found 582 (M+H,19%).

Step D 3-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-propanamide, mono(hydrochloride)

To a solution of 40mg (0.07mmol) of the intermediate obtained in Step C in 2mL methanol at room temperature was added 0.5mL of concentrated hydrochloric acid and the mixture stirred for 16 hours. All volatiles were removed under vacuum and the residue further dried under high vacuum to afford 35mg (0.07mmol, 100%) of the title compound as a pale yellow glass. ^1H NMR (200MHz, CD_3OD): 2.0-2.8 (m,6H), 3.22 (t,6Hz,2H), 4.30 (dd;7,10Hz;1H), 4.83 (d,16Hz,1H), 5.17 (d,16Hz,1H), 6.97 (d,8Hz,2H), 7.1-7.6 (m,10H). FAB-MS: calc. for $C_{27}H_{27}N_7O_2$ 481; found 482 (M+H,100%).

Example 3

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-(phenylmethyl)-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-(phenylmethyl)-1H-1-benzazepin-3(R)-yl]-butanamide

To a solution of 40mg (0.098mmol) of 3-benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 1, Step F) in 0.5mL of dry dimethylformamide at room temperature under nitrogen was added 5mg of 60% sodium hydride oil dispersion (3mg NaH, 0.13mmol, 1.3eq). After 5 minutes, 0.013mL of benzyl bromide (19mg, 0.11mmol, 1.1eq) was added and the mixture stirred for 1 hour at room temperature, then added to 20mL of ethyl acetate and washed with water (2x) and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate/hexane (1:1) to afford 44mg (0.88mmol, 90%) of product. ^1H NMR (200MHz, $CDCl_3$): 1.37 (s,3H), 1.38 (s,3H), 1.73 (m,1H), 2.3-2.6 (m,5H), 4.48 (m,1H), 4.80 (d,15Hz,1H), 5.07 (br s,2H), 5.23 (d,15Hz,1H), 5.62 (br s,1H), 6.67 (br d,7Hz,1H), 7.1-7.4 (m,14H). FAB-MS: calculated for $C_{30}H_{33}N_3O_4$ 499; found 500 (M+H,100%).

Step B: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-(phenylmethyl)-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The intermediate obtained in Step A (17mg, 0.034mmol) dissolved in 2mL of methanol was hydrogenated for 6 hours at room temperature and one atmosphere over 5mg of $Pd(OH)_2$ on carbon. The mixture was filtered through Celite and the filtrate concentrated under vacuum. The residue was purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol to 80% methanol over 10 minutes) to afford 13mg (0.027mmol, 80%) of the title compound. ^1H NMR (200MHz, CD_3OD): 1.32 (s,3H), 1.35 (s,3H), 2.0-2.6 (m,6H), 4.35 (dd;7,11Hz;1H), 4.82 (d,15Hz,1H), 5.13 (d,15Hz,1H), 7.1-7.4 (m,9H). FAB-MS: calculated for $C_{22}H_{27}N_3O_2$ 365; found 366 (m+H,100%).

Example 4

2(R)-Amino-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoroacetate)

Step A 3(R)-t-Butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

To a solution of 400mg (2.27mmol) 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1, Step B) in 5mL methylene chloride at room temperature was added 0.57mL (540mg, 2.48mmol, 1.1eq) of di-t-butyl dicarbonate. The mixture was stirred for 3 hours at room temperature then all volatiles were removed under vacuum to give 625mg (2.26mmol, 100%) of an oil that slowly solidified upon standing. ^1H NMR (200MHz,

$CDCl_3$): 1.40 (s,9H), 2.00 (m,1H), 2.65 (m,2H), 2.95 (m,1H), 4.29 (m,1H), 5.42 (br d,8Hz,1H), 6.97 (d,7Hz,1H), 7.2 (m,3H), 7.50 (br s,1H).

Step B 3(R)-t-Butoxycarbonylamino-2,3,4,5-tetrahydro-1-[[2'-[N-(triphenylmethyl)-1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-2-one

To a solution of 310mg (1.12mmol) of the intermediate obtained in Step A in 2mL dry dimethylformamide at room temperature under nitrogen was added 54mg of 60% sodium hydride oil dispersion (32mg NaH, 1.3mmol, 1.2eq). After 15 minutes, a solution of 750mg (1.34mmol, 1.2eq) N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole in 2mL dry dimethylformamide was added and the mixture stirred for 2 hours. The reaction mixture was added to 50mL of ethyl acetate and washed with pH 7.0 phosphate buffer (2x) and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed under vacuum. Purification by medium pressure liquid chromatography on silica, eluting with hexane/ethyl acetate (2:1), afforded 815mg (1.08mmol, 96%) of product. ^1H NMR (200MHz, $CDCl_3$): 1.40 (s,9H), 1.80 (m,1H), 2.40 (m,3H), 4.24 (m,1H), 4.65 (d,15Hz,1H), 5.08 (d,15Hz,1H), 5.45 (br d,7Hz,1H), 6.9-7.5 (m,26H), 7.8 (m,1H).

Step C 3(R)-Amino-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one, mono(hydrochloride)

A solution of 407mg (0.54mmol) of the intermediate obtained in Step B in 5mL methanol was hydrogenated at room temperature and 1 atmosphere over 40mg of 20% $Pd(OH)_2$ on carbon for 3 hours. The mixture was filtered through Celite and concentrated under vacuum to give a residue that was purified by medium pressure liquid chromatography on silica eluting with 2% methanol/ethyl acetate. The intermediate thus obtained (260mg) was dissolved in 5mL of methanol and treated with 1mL concentrated hydrochloric acid. After 16 hours, all volatiles were removed under vacuum to afford 226mg (0.51mmol, 94%) of product.

Step D 2(R)-(t-Butoxycarbonyl)amino-3-(t-butoxy)-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide

To a suspension of 60mg (0.13mmol) of the intermediate obtained in Step C in 2mL of methylene chloride at room temperature was added 65mg (0.15mmol, 1.1eg) of BOC-D-serine t-butyl ether dicyclohexylamine salt, followed by 0.037mL of triethylamine (27mg, 0.26mmol, 2eq) and 89mg of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.20mmol, 1.5eq). After 1 hour at room temperature, all volatiles were removed under vacuum. The residue was purified by medium pressure liquid chromatopraphy on silica, eluting with 2% methanol/ethyl acetate to afford 68mg (0.10mmol, 77%) of product. ^1H NMR (200MHz, $CDCl_3$): 1.15 (s,9H), 1.32 (s,9H), 1.88 (m,1H), 2.54 (m,3H), 3.36 (dd;6,9Hz;1H), 3.72 (m,1H), 4.10 (m,1H), 4.45 (m,1H), 4.89 (d,15Hz,1H), 5.05 (d,15Hz,1H), 5.38 (br d,7Hz,1H), 7.00 (d,8Hz,2H), 7.1-7.6 (m,9H), 7.90 (m,1H). FAB-MS: calc. for $C_{36}H_{43}N_7O_5$ 653; found 654 (M+H,8%).

Step E 2(R)-Amino-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoroacetate)

A solution of 65mg (0.099mmol) of the intermediate obtained in Step D in 2mL methylene chloride at room temperature was treated with 0.1mL of anisole followed by 1mL anhydrous trifluoroacetic acid. After 2 hours, all volatiles were removed under vacuum and the residue purified by reverse phase HPLC on C-18 eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 55% methanol to 75% methanol over 10 minutes). to afford 54mg (0.088mmol, 89%) of the title compound. ^1H NMR (200MHz, CD_3OD): 2.10 (m,1H), 2.2-2.7 (m,3H), 3.93 (m,2H), 4.38 (dd;8,12Hz;1H), 4.85 (d,14Hz,1H), 5.29 (d,14Hz,1H), 7.01 (d,8Hz,2H), 7.1-7.4 (m,6H), 7.5-7.7 (m,4H). FAB-MS: calc. for $C_{27}H_{27}N_7O_3$ 497; found 498 (M+H,100%).

Example 5

2(R)-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-pentanamide, mono(trifluoroacetate)

Step A N-(t-butoxycarbonyl)-D-norvaline

D-Norvaline (2.0g, 17.0mmol) suspended in 5mL methylene chloride was treated with 4.3mL of di-t-butyl-

dicarbonate (4.1g, 18.7mmol, 1.1eq) followed by 4.8mL of triethylamine (3.5g, 34mmol, 2eq). The mixture was stirred at room temperature for 20 hours then added to 100mL ethyl acetate and washed with 5% citric acid (2x) and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvent removed under vacuum to afford 3.55g of the product as a clear, viscous gum. ^{1}H NMR (200MHz, $CDCl_3$): 1.00 (t,7Hz,3H), 1.51 (s,9H), 1.5-2.0 (m,4H), 4.35 (m,1H), 5.08 (m,1H).

Step B 2(R)-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-pentanamide, mono(trifluroacetate)

The title compound was prepared from N-(t-butoxycarbonyl)-D-norvaline and 3(R)-amino-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one hydrochloride (Example 4, Step C), using the procedures described in Example 4, Steps D and E. ^{1}H NMR (200MHz, CD_3OD): 0.96 (t,7Hz,3H), 1.45 (m,2H), 1.80 (m,2H), 2.0-2.6 (m,4H), 3.81 (t,7Hz,1H), 4.36 (dd;7,11Hz;1H), 4.8 (d,15Hz,1H), 5.22 (d,15Hz,1H), 6.96 (d,8Hz,2H), 7.1-7.3 (m,6H), 7.4-7.7 (m,4H). FAB-MS: calc. for $C_{29}H_{31}N_7O_2$ 509; found 510 (M+H,100%).

Example 6

2(R)-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

The title compound was prepared from N-(t-butoxycarbonyl)-D-valine and 3(R)-amino-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one hydrochloride (Example 4, Step C), using the procedures described in Example 4, Steps D and E. ^{1}H NMR (200MHz, CD_3OD): 1.05 (d,7Hz,3H), 1.09 (d,7Hz,3H), 2.0-2.6 (m,5H), 3.68 (d,5Hz,1H), 4.40 (dd;7,11Hz;1H), 4.8 (d,15Hz,1H), 5.23 (d,15Hz,1H), 6.98 (d,8Hz,2H), 7.1-7.3 (m,6H), 7.4-7.7 (m,4H). FAB-MS: calc. for $C_{29}H_{31}N_7O_2$ 509; found 510 (M+H,100%).

Example 7

2(R)-Amino-3-phenyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoro acetate)

Step A 2(R)-t-Butoxycarbonylamino-3-phenyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-propanamide

To a solution of 30mg (0.17mmol) 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1; Step B) in 2mL methylene chloride at room temperature was added 50mg (0.19mmol, 1.1eq) N-(t-butoxycarbonyl)-D-phenylalanine followed by 0.047mL (34mg, 0.34mmol, 2eq) of triethylamine and 113mg (0.26mmol, 1.5eq) benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate. After 2 hours at room temperature, the mixture was added to 30mL of ethyl acetate and washed with 5% citric acid (2x), saturated aqueous sodium bicarbonate and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate to afford 71mg (0.17mmol, 100%) of the product. ^{1}H NMR (200MHz, $CDCl_3$): 1.38 (s,9H), 1.9 (m,1H), 2.6-3.1 (m,5H), 4.44 (m,2H), 5.10 (br d,7Hz,1H), 6.95 (d,8Hz,1H), 7.1-7.3 (m,8H), 8.33 (br s,1H). FAB-MS: calc. for $C_{24}H_{29}N_3O_4$ 423; found 424 (M+H,65%).

Step B 2(R)-t-Butoxycarbonylamino-3-phenyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide

To a solution of 70mg (0.17mmol) of the intermediate obtained in Step A in 0.5mL dry dimethylformamide at room temperature under nitrogen was added 8mg of 60% sodium hydride oil dispersion (5mg NaH, 0.2mmol, 1.2eq). After 10min., a solution of 120mg (0.21mmol, 1.3eq) N-triphenylmethyl-5-(4'-bromomethylbiphen-2-yl)tetrazole in 0.5mL dimethylformamide was added and the mixture stirred at room temperature for 1 hour. The reaction mixture was added to 30mL of ethyl acetate/hexane (1:1) and washed with pH 7.0 phosphate buffer and once with brine. The organic layer was removed, dried over magnesium sulfate filtered and solvents removed under vacuum. The residue was purified by medium pressure liquid chromatopraphy on silica, eluting with ethyl acetate/hexane (2:1) to afford 139mg (0.15mmol, 93%) of the product. ^{1}H NMR (200MHz, $CDCl_3$): 1.40 (s,9H), 1.67 (m,1H), 2.3-2.7 (m,3H), 3.02 (d,6Hz,2H), 4.37 (m,2H), 4.72 (d,15Hz,1H), 4.90 (br d,1H), 5.05

(d,15Hz,1H), 6.9-7.5 (m, approx. 30H), 7.86 (m,1H).

Step C 2(R)-Amino-3-phenyl-N-[2,3,4,5-tetrahydro-2-oxo--1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide mono(trifluoroacetate)

A solution of 139mg (0.15mmol) of the intermediate obtained in Step B in 5mL methanol was hydrogenated over 30mg of 20% $Pd(OH)_2$ on carbon at one atmosphere for 3 hours. The mixture was filtered through Celite and the filtrate concentrated under vacuum. The residue was redissolved in 2mL methylene chloride and the solution treated with 0.1mL of anisole followed by 1mL trifluoroacetic acid. After 2 hours at room temperature, all volatiles were removed under vacuum and the residue purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 80% methanol over 10 minutes) affording 82mg (0.12mmol, 79%) of the title compound. ^{1}H NMR (200MHz, CD_3OD): 2.1 (m,1H), 2.3-2.6 (m,3H), 3.00 (dd;9,14Hz;1H), 3.33 (dd;5,14Hz;1H), 4.13 (dd;5,9Hz;1H), 4.38 (dd;7,11Hz;1H), 4.89 (d,15Hz,1H), 5.18 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.1-7.4 (m,11H), 7.45-7.70 (m,4H). FAB-MS: calc. for $C_{33}H_{31}N_7O_2$ 557; found 558 (M+H,100%).

Example 8

2(R)-Amino-4-phenyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

The title compound was prepared from 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1; Step B) and N-(t-butoxycarbonyl)-D-homophenylalanine by the procedures described in Example 7. ^{1}H NMR (200MHz, CD_3OD): 2.1 (m,3H), 2.2-2.6 (m,3H), 2.75 (m,2H), 3.94 (t,7Hz,1H), 4.30 (dd;7,11Hz;1H), 4.84 (d,15Hz,1H), 5.22 (d,15Hz,1H), 6.97 (d,8Hz,2H), 7.1-7.7 (m,15H). FAB-MS: calc. for $C_{34}H_{33}N_7O_2$ 571; found 572 (M+H,100%).

Example 9

2(R)-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoroacetate

The title compound was prepared from 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1; Step B) and N-(t-butoxycarbonyl)-D-alanine by the procedures described in Example 7. ^{1}H NMR (200MHz, CD_3OD): 1.51 (d,7Hz,3H), 2.0-2.6 (m,4H), 3.90 (q,7Hz,1H), 4.36 (dd;7,12Hz;1H), 4.82 (d,15Hz,1H), 5.23 (d,15Hz,1H), 6.98 (d,8Hz,2H), 7.10-7.35 (m,6H), 7.45-7.70 (m,4H). FAB-MS: calc for $C_{27}H_{27}N_7O_2$ 481; found 482 (M+H,100%).

Example 10

2(S)-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoroacetate)

The title compound was prepared from 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1; Step B) and N-(t-butoxycarbonyl)-L alanine by the procedures described in Example 7. ^{1}H NMR (200MHz, CD_3OD): 1.42 (d,7Hz,3H), 2.0-2.6 (m,4H), 3.92 (q,7Hz,1H), 4.31 (dd;7,12Hz;1H), 4.88 (d,15Hz,1H), 5.19 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.10-7.35 (m,6H), 7.45-7.70 (m,4H). FAB-MS: calc. for $C_{27}H_{27}N_7O_2$ 481; found 482 (M+H,100%).

Example 11

2(R)-Methylamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoroacetate)

The title compound was prepared from 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1; Step B) and N-methyl-N-(t-butoxycarbonyl)-D-alanine by the procedures described in Example 7. ^{1}H NMR (200MHz, CD_3OD): 1.52 (d,7Hz,3H), 2.0-2.6 (m,4H), 2.60 (s,3H), 3.81 (q,7Hz,1H), 4.36 (dd;8,12Hz;1H), 4.85 (d,15Hz,1H), 5.22 (d,15Hz,1H), 6.98 (d,8Hz,2H), 7.10-7.35 (m,6H), 7.45-7.70 (m,4H). FAB-MS: calc. for

$C_{28}H_{29}N_7O_2$ 495; found 496 (M+H,100%).

Example 12

2(R)-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

Step A: 2(R)-(t-Butoxycarbonylamino)butanoic acid

(R)-2-Aminobutanoic acid (1.03g, 10.0mmol) suspended in 5mL methylene chloride was treated with 2.3mL of di-t-butyl-dicarbonate (2.18g, 10.0mmol, 1eq) and 4mL of diisopropylethylamine (2.83g, 23mmol, 2.3eq). The mixture was stirred at room temperature for 16 hours then extracted with 30mL saturated aqueous sodium bicarbonate. The aqueous layer was washed with 20mL of methylene chloride then removed and acidified to pH 2 by dropwise addition of saturated aqueous potassium hydrogen sulfate. The mixture was extracted with ethyl acetate (2x20mL); the combined extracts were dried over magnesium sulfate, filtered and solvents removed under vacuum to afford 451mg (2.2mmol, 22%) of product. ^{1}H NMR (200MHz, $CDCl_3$): 0.93 (t,8Hz,3H), 1.40 (s,9H), 1.6-2.0 (m,2H), 4.25 (m,1H), 5.10 (br d,7Hz,1H), 6.45 (br s,1H).

Step B:

The title compound was prepared from the intermediate obtained in Step A and 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1; Step B) by the procedures described in Example 7. ^{1}H NMR (200MHz, CD_3OD): 1.05 (t,7Hz,3H), 1.8-2.6 (m,6H), 3.78 (t,6Hz,1H), 4.38 (m,1H), 4.82 (d,15Hz,1H), 5.23 (d,15Hz,1H), 6.98 (d,8Hz,2H), 7.10-7.35 (m,6H), 7.45-7.70 (m,4H). FAB-MS: calc. for $C_{28}H_{29}N_7O_2$ 495; found 496 (M+H,77%).

Example 13

2(R)-Amino-3-[indol-3-yl]-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoro acetate)

Step A 2(R)-t-Butoxycarbonylamino-3-[N-formyl-(indol-3-yl)]-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-1H-tetrazol-5-yl]-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-(R)-yl]-propanamide

This intermediate was prepared from N_a-t-butoxycarbonyl-N'-formyl-D-tryptophan and 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1; Step B) by the procedures described in Example 7, Steps A and B ^{1}H NMR (200MHz, $CDCl_3$): 1.43 (s,9H), 2.3-2.5 (m,4H), 3.09 (dd;8,13Hz;1H), 3.28 (m,1H), 4.4 (m,2H), 4.73 (d,15Hz,1H), 4.94 (d,15Hz,1H), 5.2 (br s,1H), 6.65 (d,7Hz,1H), 6.9-7.5 (m, approx. 30H), 7.56 (d,8Hz,1H), 7.84 (m,1H), 8.18 (br s,1H).

Step B: 2(R)-Amino-3-[indol-3-yl]-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoroacetate)

A solution of 125mg (0.13mmol) of the intermediate obtained in Step A in 2mL of methanol was hydrogenated at room temperature and one atmosphere over 30mg of 20% $Pd(OH)_2$ on carbon for 3 hours. The mixture was filtered through Celite and solvent removed under vacuum. The residue was redissolved in 2mL of methylene chloride and treated with 0.1mL of anisole followed by 1mL of trifluoroacetic acid. After 1 hour at room temperature, all volatiles were removed under vacuum and the residue redissolved in 2mL of methanol and treated with 0.5mL of concentrated hydrochloric acid. The mixture was treated at 60°C for 2 hours then all volatiles were removed under vacuum. The residue was purified by reverse-phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 55% methanol increased to 75% methanol over 10 minutes) to afford 68mg (0.096mmol, 74%) of the title compound. ^{1}H NMR (200MHz, CD_3OD): 2.0 (m,1H), 2.2-2.6 (m,3H), 3.20 (dd;8,13Hz;1H), 3.44 (dd;6,13Hz;1H), 4.14 (dd;6,8Hz;1H), 4.29 (dd;6,11Hz;1H), 4.76 (d,15Hz,1H), 5.22 (d,15Hz,1H), 6.9-7.7 (m,17H). FAB-MS: calc. for $C_{35}H_{32}N_8O_2$ 596; found 597 (M+H,100%).

Example 14

2(R)-Amino-3-[imidazol-4-yl]-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoroacetate)

Step A 2(R)-t-Butoxycarbonylamino-3-[N-tosyl-(imidazol-4-yl)]-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-propanamide

Prepared from N_a-t-butoxycarbonyl-N_{im}-tosyl-D-histidine and 3(R)-amino-2,3,4,5-tetrahydro1H-1-benzazepin-2-one (Example 1; Step B) by the procedure described in Example 7, Step A. ^{1}H NMR (200MHz, $CDCl_3$): 1.38 (s,9H), 1.70 (m,1H), 2.42 (s,3H), 2.5-2.9 (m,5H), 4.42 (m,2H), 5.77 (br s,1H), 6.95 (d,7Hz,1H), 7.05 (s,1H), 7.1-7.3 (m,3H), 7.33 (d,8Hz,2H), 7.58 (br d,7Hz,1H), 7.79 (d,8Hz,2H), 7.90 (s,1H), 8.40 (br s,1H). FAB-MS: calc. for $C_{28}H_{33}N_5O_6S$ 567; found 568 (M+H,100%).

Step B 2(R)-t-Butoxycarbonylamino-3-[N-tosyl-(imidazol-4-yl)]-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]1H-1-benzazepin-3(R)-yl]-propanamide

Prepared from the product obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 7, Step B. ^{1}H NMR (200MHz,$CDCl_3$): 1.43 (s,9H), 2.2-2.4 (m,4H), 2.40 (s,3H), 2.83 (dd;5,14Hz;1H), 3.05 (dd;6,14Hz;1H), 4.35 (m,2H), 4.63 (d,14Hz,1H), 5.12 (d,14Hz,1H), 5.88 (br s,1H), 6.9-7.5 (m,approx. 28H), 7.75-7.95 (m,4H).

Step C: 2(R)-Amino-3-[imidazol-4-yl]-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoroacetate)

A solution of 104mg (0.10mmol) of the intermediate obtained in Step B in 2mL of chloroform at room temperature was treated with 27mg (0.20mmol, 2eq) of 1-hydroxybenzotriazole hydrate. After 14 hours, the solvent was removed under vacuum and the residue redissolved in 2mL of methanol and hydrogenated at one atmosphere over 20mg of 20% $Pd(OH)_2$/C for 3 hours. The mixture was filtered through Celite and solvent removed under vacuum. The residue was redissolved in 2mL of methylene chloride and treated with 0.1mL of anisole followed by 1mL of trifluoroacetic acid. After 2 hours at room temperature, all volatiles were removed under vacuum and the residue purified by reverse-phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 45% methanol increased to 65% methanol over 10 minutes) to afford 56mg (0.085mmol, 85%) of the title compound. ^{1}H NMR (200MHz, CD_3OD): 2.15-2.50 (m,4H), 3.38 (dd;6,12Hz;1H), 3.51 (dd;4,12Hz;1H), 4.24 (dd;4,6Hz;1H), 4.38 (dd;8,12Hz;1H), 5.12 (s,2H), 7.03 (d,8Hz,2H), 7.2-7.4 (m,6H), 7.4-7.7 (m,5H), 8.61 (s,1H). FAB-MS: calc. for $C_{30}H_{29}N_9O_2$ 547; found 548 (M+H,77%).

Example 15

2(S)-Amino-3-[imidazol-4-yl]-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoroacetate)

The title compound was prepared from N_a-t-butoxycarbonyl-N_{im}-tosyl-L-histidine, dicyclohexylamine salt and 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1; Step B) by the procedures described in Example 14. ^{1}H NMR (200MHz, CD_3OD): 1.9-2.6 (m,4H), 3.25 (m,2H), 4.16 (t,7Hz,1H), 4.31 (dd;7,11Hz;1H), 4.88 (d,15Hz,1H), 5.17 (d,15Hz,1H), 6.99 (d,8Hz,2H), 7.1-7.6 (m,11H), 8.82 (s,1H). FAB-MS: calc. for $C_{30}H_{29}N_9O_2$ 547; found 548 (M+H,81%).

Example 16

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-methyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

Step A: 3-(t-Butoxycarbonylamino)-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

A solution of 50mg (0.080mmol) of 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-(R)-yl]-butanamide trifluoroacetate (Example 1) in 2mL of

methylene chloride at room temperature was treated with 0.017mL of triethylamine (12mg, 0.12mmol, 1.5eq) followed by 0.021mL of di-t-butyl-dicarbonate (20mg, 0.091mmol, 1.1eq). The mixture was stirred for 14 hours then all volatiles were removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate/acetonitrile/methanol (9:1:.5) to afford 42mg of product (0.069mmol, 86%). ^{1}H NMR (200MHz, CD_3OD): 1.25 (s,6H), 1.45 (s,9H), 2.0 (m,1H), 2.2-2.6 (m,5H), 4.32 (m,1H), 4.78 (d,14Hz,1H), 5.26 (d,14Hz,1H), 6.97 (d,8Hz,2H), 7.10-7.35 (m,6H), 7.40-7.60 (m,4H). FAB-MS: calculated for $C_{34}H_{39}N_7O_4$ 609; found 610 (M+H, 22%).

Step B: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-methyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

A solution of 42mg (0.070mmol) of the intermediate obtained in Step A in 2mL of methylene chloride at room temperature was treated with a diethyl ether solution of diazomethane until a yellow color persisted. Glacial acetic acid (0.2mL) was added and all volatiles removed under vacuum. The residue was redissolved in 2mL of methylene chloride and treated with 0.1mL of anisole followed by 0.5mL of trifluoroacetic acid. After two hours at room temperature, all volatiles were removed under vacuum and the residue purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient; 75% methanol increased to 85% methanol over ten minutes). Two components were isolated: the title compound elutes first and 26mg (0.041mmol, 59%) was thus obtained. This was followed by the N_2 isomer (8mg, 0.013mmol, 18%) described in Example 17. ^{1}H NMR (200MHz, CD_3OD): 1.33 (s,3H), 1.37 (s,3H), 2.0-2.6 (m,6H), 3.13 (s,3H), 4.34 (dd;7,11Hz;1H), 4.77 (d,14Hz,1H), 5.37 (d,14Hz,1H), 6.98 (d,8Hz,2H), 7.1-7.4 (m,6H), 7.5-7.8 (m,4H). FAB-MS: calc. for $C_{30}H_{33}N_7O_2$ 523; found 524 (M+H,100%).

Example 17

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(2-methyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

The title compound was obtained from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide trifluoroacetate (Example 1) by the procedures described in Example 16. ^{1}H NMR (200MHz, CD_3OD): 1.32 (s,3H), 1.36 (s,3H), 2.0-2.6 (m,6H), 4.21 (s,3H), 4.37 (dd;8,12Hz;1H), 4.87 (d,15Hz,1H), 5.22 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.1-7.6 (m,9H), 7.69 (d,8Hz,1H). FAB-MS: calc. for $C_{30}H_{33}N_7O_2$ 523; found 524 (M+H,100%).

Example 18

3-(2-Benzyloxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

To a stirred solution of 50mg (0.080mmol) 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide trifluoroacetate (Example 1) in 3mL of absolute methanol was added 0.022mL (16mg, 0.16mmol, 2eq) of triethylamine followed by 120mg of powdered 3A molecular sieves. To this stirred mixture was added a solution of 0.012mL (12mg, 0.08mmol, 1eq) of benzyloxyacetaldehyde (prepared from 2,3-O-isopropylideneglycerol by the method of Shiao,et al, Synth. Comm., 18, 359 (1988)) in 2mL dry methanol. The pH of the reaction mixture was adjusted to 7.5 (paper) by the addition of triethylamine and trifluoroacetic acid and was stirred for two hours. To this was added 0.48mL of a 1M solution of sodium cyanoborohydride in tetrahydrofuran (0.48mmol, 6eq). The reaction mixture was stirred at room temperature for 24 hours then filtered and the filtrate treated with 2mL of glacial acetic acid. After concentration under vacuum, the residue was purified by reverse phase HPLC on C-18, eluting with methanol/0.1°% aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 80% methanol in 10 minutes) to afford 35mg (0.046mmol, 58%) of the title compound. ^{1}H NMR (200MHz, CD_3OD): 1.34 (s,3H), 1.36 (s,3H), 2.0-2.6 (m,6H), 3.20 (t,5Hz,2H), 3.70 (t,5Hz,2H), 4.38 (dd;7,11Hz;1H), 4.52 (s,2H), 4.93 (d,15Hz,1H), 5.11 (d,15Hz,1H), 6.98 (d,8Hz,2H), 7.1-7.3 (m,11H), 7.4-7.6 (m,4H). FAB-MS: calc. for $C_{38}H_{41}N_7O_3$ 643; found 644 (M+H,100°%).

Example 19

3-(2-hydroxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

A solution of 12mg (0.016mmol) of 3-(2-benzyloxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2--oxo-1-[[2'-(1Htetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide trifluoroacetate (Example 18) in 12mL of absolute methanol was hydrogenated at room temperature and 40psi over 30% Pd/C for 24 hours. The mixture was filtered through Celite and the filtrate concentrated under vacuum. The residue was purified by reverse phase HPLC on C-18, eluting with methanol/0.1%aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 80% methanol in 10 minutes) to afford 6.3mg (0.0094mmol, 59%) of the title compound. ^{1}H NMR (200MHz, CD_3OD): 1.35 (s,3H), 1.38 (s,3H), 2.0-2.6 (m,6H), 3.09 (t,5Hz,2H), 3.73 (t,5Hz,2H), 4.33 (dd;7,11Hz;1H), 4.90 (d,15Hz,1H), 5.13 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.1-7.4 (m,6H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{31}H_{35}N_7O_3$ 553; found 554 (M+H,100%).

Example 20

3-(2-Hydroxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[1-(2-hydroxyethyl)-tetrazol-5-yl-][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

Step A: 3-(2-Benzyloxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[1-(2-hydroxyethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanimide, mono(trifluoroacetate) and 3-(2-Benzyloxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[-2'-[2-(2-hydroxyethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanimide, mono(trifluoroacetate)

To a solution of 40mg (0.053mmol) of 3-(2-benzyloxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide mono(trifluoroacetate) (Example 18) in 3mL of methanol was added a catalytic amount of pyridinium p-toluenesulfonate. Ethylene oxide was bubbled through the solution for five minutes; the flask was capped tightly and the solution stirred at room temperature for 24 hours. All volatiles were removed under vacuum and the residue purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 85% methanol in 10 minutes) to afford 18mg (0.022mmol, 42%) of the N_1 product followed by 6mg (0.0075mmol, 14%) of the N_2 product. ^{1}H NMR (200MHz, CD_3OD): 1.35 (s,3H), 1.38 (s,3H), 2.0-2.6 (m,6H), 3.22 (t,5Hz,2H), 3.54 (m,4H), 3.71 (t,5Hz,2H), 4.37 (dd;7,11Hz;1H), 4.55 (s,2H), 4.86 (d,15Hz,1H), 5.22 (d,15Hz,1H), 6.95 (d,8Hz,2H), 7.1-7.4 (m,11H), 7.5-7.8 (m,4H). FAB-MS: calc. for $C_{40}H_{45}N_7O_4$ 687; found 688 (M+H,100%).

Step B: 3-(2-Hydroxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[1-(2-hydroxyethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

A solution of 18mg (0.022mmol) of the N1 intermediate obtained in Step A in methanol was hydrogenated at room temperature and 40psi over 30% Pd/C for 24 hours. The mixture was filtered and concentrated under vacuum. The residue was purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 55% methanol increased to 85% methanol in 10 minutes) to afford 12mg (0.017mmol, 75%) of the title compound. ^{1}H NMR (200MHz, CD_3OD): 1.35 (s,3H), 1.38 (s,3H), 2.0-2.6 (m,6H), 3.09 (t,5Hz,2H), 3.56 (br s,4H), 3.73 (t,5Hz,2H), 4.32 (dd;8,12Hz;1H), 4.81 (d,15Hz,1H), 5.28 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.1-7.3 (m,6H), 7.-7.7 (m,4H). FAB-MS: calc. for $C_{33}H_{39}N_7O_4$ 597; found 598 (M+H,100%).

Example 21

3-(2-Hydroxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[2-(2-hydroxyethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanimide, mono(trifluoroacetate)

Step A: 3-(2-Benzyloxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[2-(2-hydroxyethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanimide, mono(trifluoroacetate)

Prepared from 3-(2- benzyloxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-(R)-yl]-butanamide, mono(trifluoroacetate) (Example 18) by

the procedures described in Example 20, Step A. ^{1}H NMR (200MHz, CD_3OD): 1.32 (s,3H), 1.36 (s,3H), 2.0-2.7 (m,6H), 3.19 (t,5Hz,2H), 3.66 (t,5Hz,2H), 3.88 (t,5Hz,2H), 4.40 (dd;8,12Hz;1H), 4.50 (s,2H), 4.56 (t,5Hz,2H), 5.02 (br s,2H), 6.99 (d,8Hz,2H), 7.1-7.6 (m,15H). FAB-MS: calc. for $C_{40}H_{45}N_7O_4$ 687; found 688 (M+H,100%).

Step B: 3-(2-Hydroxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-[2-(2-hydroxyethyl)-tetrazol-5-yl][1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 20, Step B. ^{1}H NMR (200MHz, CD_3OD): 1.34 (s,3H), 1.37 (s,3H), 2.0-2.7 (m,6H), 3.08 (t,5Hz,2H), 3.72 (t,5Hz,2H), 3.90 (t,5Hz,2H), 4.35 (dd;8,12Hz;1H), 4.59 (t,5Hz,2H), 4.96 (d,15Hz,1H), 5.10 (d,15Hz,1H), 7.02 (d,8Hz,2H), 7.1-7.7 (m,10H). FAB-MS: calc. for $C_{33}H_{39}N_7O_4$ 597; found 598 (M+H,67%).

Example 22

3-(2-Hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

Step A: 3-(2-Benzyloxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

This intermediate was prepared as a mixture of diastereomers (at the carbinol carbon) from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide trifluoroacetate (Example 1) and (+/-) 2-benzyloxypropionaldehyde [prepared from 3-buten-2-ol by the method of Shiao,et al, Synth. Comm., 18, 359 (1988)] by the procedure described in Example 18, Step A. ^{1}H NMR (200MHz, CD_3OD): 1.24 (m,3H), 1.34 (m,6H), 2.0-2.6 (m,6H), 2.93 (dd;9,12Hz;1H), 3.16 (dd;3,12Hz;1H), 3.80 (m,1H), 4.40 (m,2H), 4.62 (m,2H), 4.8-5.2 (m,2H), 6.9-7.6 (m,17H). FAB-MS: calc. for $C_{39}H_{43}N_7O_3$ 657; found 658 (M+H,100%).

Step B: 3-(2-Hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 19. ^{1}H NMR (200MHz, CD_3OD): 1.20 (d,7Hz,3H), 1.35 (m,6H), 2.0-2.7 (m,6H), 2.75 (m,1H), 3.07 (dd;3,12Hz;1H), 3.91 (m,1H), 4.33 (dd;8,12Hz;1H), 4.9 (m,1H), 5.2 (m,1H), 7.02 (d,8Hz,2H), 6.9-7.6 (m,12H). FAB-MS: calc. for $C_{32}H_{37}N_7O_3$ 567; found 568 (M+H,100%).

Example 23

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-[1-(2-hydroxyethyl)-tetrazol-5-yl][1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

Step A: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-[1-(2-hydroxyethyl)-tetrazol-5-yl]-[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanimide, mono(trifluoroacetate)

To a solution of 54mg (0.099mmol) of 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide mono(trifluoroacetate) (Example 1) in 2mL of methylene chloride was added a catalytic amount of pyridinium p-toluenesulfonate. Ethylene oxide was bubbled through the solution for five minutes; the flask was capped tightly and the solution stirred at room temperature for 24 hours. All volatiles were removed under vacuum and the residue purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 80% methanol in 10 minutes) to afford 37mg (0.055mmol, 56%) of the title compound followed by 15mg (0.022mmol, 22%) of the N2 product. ^{1}H NMR (200MHz, CD_3OD): 1.32 (s,3H), 1.36 (s,3H), 2.0-2.6 (m,6H), 3.55 (m,4H), 4.33 (dd;7,11Hz;1H), 4.79 (d,14Hz,1H), 5.31 (d,14Hz,1H), 6.99 (d,8Hz,2H), 7.1-7.3 (m,6H), 7.5-7.8 (m,4H). FAB-MS: calc. for $C_{31}H_{35}N_7O_3$ 553; found 554 (M+H,100%).

Example 24

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[2-(2-hydroxyethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-([2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-1-benzazepin-3(R)-yl]-butanamide mono(trifluoroacetate) (Example 1) by the procedure described in Example 23. ^{1}H NMR (200MHz, CD_3OD): 1.33 (s,3H), 1.36 (s,3H), 2.0-2.6 (m,6H), 3.90 (t,5Hz,2H), 4.37 (dd;8,12Hz;1H), 4.60 (d,5Hz,2H), 4.91 (d,15Hz,1H), 5.17 (d,15Hz,1H), 7.01 (d,8Hz,2H), 7.1-7.6 (m,9H), 7.75 (d,7Hz,1H). FAB-MS: calc. for $C_{31}H_{35}N_7O_3$ 553; found 554 (M+H,100%).

Example 25

2-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-acetamide, hydrochloride

Step A: 3-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-acetamide

To a solution of 169mg (0.965 mmol) of N-(t-butoxycarbonyl) glycine in 2mL of methylene chloride at room temperature was added 222mg (1.158 mmol, 1.2eq) of 1-(3-dimethylominopropyl)-3-ethylcarbodiimide hydrochloride, 11mg (0.09mmol, 0.1eq) of 4-dimethylominopyridine and 170mg (0.97 mmol, 1eq) of 3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Example 1, Step A). The reaction was stirred at room temperature for 3 hours. The reaction was then quenched by the addition of 5mL of 1M aqueous hydrochloric acid, and the aqueous phase extracted with methylene chloride (2x5mL). The combined organic phases were dried over magnesium sulfate, filtered and the solvent removed under vacuum. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford 218mg (0.65mmol, 68%) of the product. ^{1}H NMR (200MHz, $CDCl_3$): 1.43 (s,9H), 1.96 (m,1H), 2.83 (m,3H), 3.81(dq;2,8Hz;2H), 4.54 (m,1H), 5.21 (t,3Hz,1H), 7.15 (m,4H), 7.84 (br s,1H). FAB-MS: calculated for $C_{17}H_{23}P_3O_4$ 333; found 334 (M+H,43%).

Step B: 2-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-acetamide

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.26 (s,9H), 1.81 (m,1H), 2.48 (m,3H), 3.80 (dq;3,9Hz;2H), 4.50 (m,1H), 4.72 (d,7Hz,1H), 5.10 (d,7Hz,1H), 6.9-7.6 (m,26H), 7.96 (m,1H).

Step C: 2-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-acetamide

323mg (0.43mmol) of the intermediate obtained in Step B was dissolved in 1mL of glacial acetic acid and 1mL of water was added dropwise with stirring. The reaction mixture was stirred at room temperature for 16 hours then solvents were removed under vacuum and the residue purified by flash chromatography on a silica gel column, eluting with ethyl acetate to afford 109mg (0.196mmol, 46%) of the product. ^{1}H NMR (200MHz, $CDCl_3$): 1.38 (s,9H), 1.97 (m,1H), 2.55 (m,3H), 3.65 (m,2H), 4.50 (m,1H), 4.85 (d,15Hz,1H), 5.05 (d,16Hz,1H), 5.51 (br s,1H) 6.95-7.95 (m,11H), 7.83 (d,3Hz,1H).

Step D: 2-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-acetamide, hydrochloride

The intermediate obtained in Step C (109mg, 0.196mmol) was dissolved in 2mL of methanol and treated with 0.1mL of concentrated hydrochloric acid. The reaction mixture was stirred at room temperature for 16 hours then solvents were removed under vacuum and the residue redissolved in water and washed with ethyl acetate. The aqueous layer was separated and the solvent removed under vacuum to yield 87mg (0.17mmol, 88%) of the title compound. ^{1}H NMR (200MHz,CD_3OD): 2.10 (m,1H), 2.48 (m,3H), 3.68 (s,2H), 4.37 (m,1H), 4.84 (d,14Hz,1H), 5.22 (d,14Hz,1H), 6.9-7.7 (m,12H). FAB-MS: calculated for $C_{26}H_{25}N_7O_2$ 467; found 468 (M+H,100%).

EXAMPLE 26

4-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, hydrochloride

Step A: 4-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Example 1, Step A) and 4-(t-butoxycarbonylamino)butyric acid by the procedure described in Example 25, Step A. ^{1}H NMR (200MHz, $CDCl_3$): 1.42 (s,9H), 1.7-2.1 (m,3H), 2.24 (t,5Hz,2H), 2.58-3.29 (m,5H), 4.57 (m,1H), 4.86 (br s,1H), 7.0-7.3 (m,4H), 8.32 (s,1H). FAB-MS: calculated for $C_{19}H_{27}N_3O_4$ 361; found 362 (M+H,60%).

Step B: 4-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.42 (s,9H), 1.78 (m,3H), 2.20 (t,5Hz,2H), 2.2-2.7 (m,2H), 3.13 (m,2H), 4.46 (m,1H), 4.70 (d,14Hz,1H), 5.10 (d,14Hz,1H), 6.64 (d,7Hz,1H), 6.8-7.5 (m,26H), 7.85 (m,1H).

Step C: 4-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide

The intermediate obtained in Step B (349mg, 0.40mmol) was dissolved in 5mL of methanol and hydrogenated at room temperature and one atmosphere over 70mg of 20% $Pd(OH)_2/C$ for 16 flours. The reaction mixture was filtered through Celite and solvent removed under vacuum. The crude product was purified by flash chromatography on silica, eluting with 10% methanol/ethyl acetate to afford 168mg (0.28mmol, 71%) of product. ^{1}H NMR (200MHz, CD_3OD): 1.41 (s,9H), 1.72 (m,2H), 2.0-2.6 (m,6H), 3.24 (t,7Hz,2H), 4.32 (m,1H), 4.85 (d,14Hz,1H), 5.20 (d,14Hz,1H), 6.9-7.7 (m,12H).

Step D: 4-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-butanamide, hydrochloride

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 25, Step D. ^{1}H NMR (200MHz, CD_3OD): 1.8-2.6 (m, H), 2.96 (t,6Hz,2H), 4.30 (m,1H), 4.88 (d,15Hz,1H), 5.25 (d,15Hz,1H), 6.9-7.4 (m,8H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{28}H_{29}N_7O_2$ 495; found 496 (M+H,100%).

Example 27

2-Amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-propanamide, hydrochloride

Step A: 2-(t-Butoxycarbonylamino)-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-propanamide

Prepared from 2-(t-butoxycarbonylamino-2-methylpropanoic acid and 3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Example 1, Step A) by the procedure described in Example 25, Step A. ^{1}H NMR (200MHz, $CDCl_3$): 1.38 (s,12H), 1.44 (s,3H), 1.90 (m,1H), 2.5-3.0 (m,3H), 4.45 (m,1H), 5.10 (s,1H), 6.97 (m,1H), 7.20 (m,3H), 8.45 (s,1H).

Step B: 2-(t-Butoxycarbonylamino)-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenyl-methyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-propanamide

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.42 (s,9H), 1.43 (s,3H), 1.47 (s,3H), 1.75 (m,1H), 2.2-2.7 (m,3H), 4.45 (m,1H), 4.71 (d,14Hz,1H), 5.10 (d,14Hz,1H), 6.9-7.5 (m,26H), 7.87 (m,1H).

Step C: 2-(t-butoxycarbonylamino)-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-propanamide

Prepared from the intermediate obtained in Step B by the procedure described in Example 26, Step C. ^{1}H NMR (200MHz, CD_3OD): 1.34 (s,6H), 1.40 (s,9H), 1.95 (m,1H), 2.44 (m,3H), 4.30 (m,1H), 4.77 (d,14Hz,1H), 5.26 (d,14Hz,1H), 6.9-7.7 (m,12H). FAB-MS: calculated for $C_{33}H_{37}N_7O_4$ 595; found 596 (M+H,40%).

Step D: 2-Amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-propanamide, hydrochloride

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 25, Step D. ^{1}H-NMR (200MHz, CD_3OD): 1.50 (s,3H), 1.62 (s,3H), 2.2-2.7 (m,4H), 4.32 (m,1H), 4.85 (d,14Hz,1H), 5.17 (d,14Hz,1H), 6.9-7.7 (m,12H). FAB-MS: calculated for $C_{28}H_{29}N_7O_2$ 495; found 496 (M+H,100°%).

Example 28

6-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3-yl]-hexanamide, hydrochloride

Step A: 6-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-hexanamide

Prepared from 6-(t-butoxycarbonylamino)-hexanoic acid and 3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Example 1, Step A) by the procedure described in Example 25, Step A. ^{1}H NMR (200 MHz, $CDCl_3$): 1.2-1.7 (m,14H), 1.92 (m,2H), 2.16 (t,5Hz,2H), 2.5-3.1 (m,6H), 4.53 (m,2H), 6.54 (d,7Hz,1H), 6.96 (m,1H), 7.18 (m,3H), 8.00 (s,1H). FAB-MS: calculated for $C_{21}H_{31}N_3O_4$ 389; found 390 (M+H,18%).

Step B: 2-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-bezazepin-3-yl]-hexanamide

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz,$CDCl_3$): 1.1-1.9 (m,16H), 2.15 (t,5Hz,2H), 2.2-2.7 (m,3H), 3.07 (q,6Hz,2H), 4.49 (m,2H), 4.70 (d,14Hz,1H), 5.11 (d,14Hz,1H), 6.49 (d,8Hz,1H), 6.8-7.5 (m,26H), 7.86 (m,1H).

Step C: 2-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-hexanamide

Prepared from the intermediate obtained in Step B by the procedure described in Example 26, Step C. ^{1}H NMR (200MHz, CD_3OD): 1.1-1.7 (m,16H), 2.0-2.6 (m,5H), 2.98 (t,2H), 4.32 (m,1H), 4.81 (d,16Hz,1H), 5.22 (d,16Hz,1H), 6.95 (m,2H), 7.23 (m,6H), 7.52 (m,4H). FAB-MS: calculated for $C_{35}H_{41}N_7O_4$ 623; found 646 (M+Na,45%).

Step D: 2-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-hexanamide, hydrochloride

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 25, Step D. ^{1}H NMR (200MHz, CD_3OD): 1.88 (m,2H), 1.63 (m,4H) 2.0-2.7 (m,6H), 2.90 (br s,2H), 4.31 (m,1H), 4.86 (d,14Hz,1H), 5.17 (d,14Hz,1H), 6.98 (d,8Hz,2H), 7.22 (m,6H), 7.56 (m,4H). FAB-MS: calculated for $C_{30}H_{33}N_7O_2$ 523; found 524 (M+H,100%).

Example 29

1-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-cyclohexanecarboxamide, hydrochloride

Step A: 1-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-cyclohexanecarboxamide

Prepared from 1-(t-butoxycarbonylamino)-cyclohexanecarboxylic acid and 3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Example 1, Step A) by the procedure described in Example 25, Step A. ^{1}H NMR (200MHz, $CDCl_3$): 1.1-2.2 (m,19H), 2.00 (m,2H), 2.50 (m,2H), 4.55 (m,1H), 6.9-7.2 (m,4H). FAB-MS: calculated for $C_{22}H_{31}N_3O_4$ 401; found 402 (M+H,40%).

Step B: 1-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-cyclohexanecarboxamide

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.1-2.1 (m,19H), 2.20 (m,4H), 4.45 (m,1H), 4.67 (s,1H), 4.72 (d,13Hz,1H), 5.06 (d,13Hz,1H), 6.8-7.5 (m,26H), 7.86 (m,1H).

Step C: 1-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-cyclohexanecarboxamide

Prepared from the intermediate obtained in Step B by the procedure described in Example 26, Step C. ^{1}H NMR (200MHz, CD_3OD): 1.2-1.9 (m,19H), 2.00 (br s,2H), 2.53 (m,3H), 4.40 (m,1H), 4.86 (d,14Hz,1H), 5.34 (d,14Hz,1H), 6.81 (br s,1H), 7.0-7.5 (m,8H), 7.60 (m,4H). FAB-MS: calculated for $C_{36}H_{41}N_7O_4$ 635; found 636 (M+H,20%).

Step D: 1-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-cyclohexanecarboxamide, hydrochloride

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 25, Step D. ^{1}H NMR (200MHz, CD_3OD): 1.6-2.4 (m,8H), 2.28 (m,4H), 2.62 (m,2H), 4.42 (m,1H), 4.96 (d,15Hz,1H), 5.26 (d,15Hz,1H), 7.0-7.5 (m,8H), 7.64 (m,4H). FAB-MS: calculated for $C_{31}H_{33}N_7O_2$ 535; found 536 (M+H,100%).

Example 30

2(S),6-Diamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-hexanamide, dihydrochloride

Step A: 2(S),6-Di-(t-butoxycarbonylamino)-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-hexanamide

Prepared from N_a,N_e-di(t-butoxycarbonyl)-L-lysine and 3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Example 1, Step A) by the procedure described in Example 25, Step A. ^{1}H NMR (200MHz, $CDCl_3$): 1.2-2.1 (m,24H), 2.6-3.3 (m,6H), 4.20 (m,1H), 4.62 (m,2H), 5.26 (m,1H), 7.0-7.4 (m,4H). FAB-MS: calculated for $C_{26}H_{40}N_4O_6$ 504; found 505 (M+H,20%).

Step B: 2(S),6-Di-(t-butoxycarbonylamino)-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-hexanamide

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.42 (s,18H), 1.60 (m,2H), 1.79 (m,2H), 2.42 (m,4H), 3.10 (m,4H), 4.09 (m,1H), 4.42 (m,1H), 4.60 (d,13Hz,1H), 5.17 (d,13Hz,1H), 6.8-7.5 (m,26H), 7.85 (m,1H).

Step C: 2(S),6-Di-(t-butoxycarbonylamino)-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-hexanamide

Prepared from the intermediate obtained in Step B by the procedure described in Example 26, Step C. ^{1}H NMR (200MHz, CD_3OD): 1.0-1.8 (m,20H), 2.00 (m,2H), 3.00 (m,2H), 3.95 (m,1H), 4.32 (m,1H), 4.76 (d,13Hz,1H), 5.26 (d,13Hz,1H), 6.9-7.4 (m,8H), 7.4-7.6 (m,4H). FAB-MS: calculated for $C_{40}H_{50}N_8O_6$ 738; found 739 (M+H,10%).

Step D: 2(S),6-diamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-hexanamide, dihydrochloride

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 25, Step D. ^{1}H NMR (200MHz, CD_3OD): 1.3-2.0 (m,6H), 2.0-2.7 (m,4H), 2.95 (m,2H), 3.95 (m,1H), 4.37 (m,1H), 4.89 (d,15Hz,1H), 5.19 (dd;4,15Hz,1H), 6.9-7.4 (m,8H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{30}H_{34}N_8O_2$ 538; found 539 (M+H,100%).

Example 31

3-amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

Step A: 7-fluoro-2, 3, 4, 5-tetrahydro-1H-1-benzazepin-2-one

Sodium azide 1.1g (16.92mmol) was added to a mixture of 6.0mL of chloroform and 1.1mL of water at 0°C. Concentrated sulfuric acid (0.44mL) was added dropwise and the mixture stirred at 0°C for two hours then filtered. The chloroform layer containing hydrazoic acid was added to a solution of 1.3g (7.92mmol) of 6-fluoro-1-tetralone (prepared by the method of Allinger and Jones, J. Org. Chem., 27, 70-76 (1962)) in 4.8mL of chloroform. Additional sulfuric acid (2.16mL) was added dropwise with stirring while maintaining the temperature below 40°C. The mixture was stirred at 40°C for two hours then at room temperature for 16 hours. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was added to ice; the resulting precipitate was extracted with methylene chloride (5x). The combined extracts were washed with brine, dried over magnesium sulfate and filtered through a silica plug. Solvents were removed under vacuum to afford 162mg (0.92mmol,11%) of the product. ^{1}H NMR (300MHz, $CDCl_3$): 2.21 (m,2H), 2.32 (t,7Hz,2H) 2.77 (t,7Hz,2H), 6.93 (m,3H), 7.8 (br s,1H). FAB-MS: calculated for $C_{10}H_{10}FNO$ 179; found 180 (M+H,100%).

Step B: 3-Iodo-7-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

7-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (411mg, 2.3mmol) (Step A) dissolved in a mixture of 7.9mL of dry methylene chloride and 1.0mL of dry tetrahydrofuran was treated with 1.62mL (1.18g, 11.6mmol, 5eq) of triethylamine and the resulting solution cooled to -15°C.
Iodotrimethylsilane (0.66mL, 932mg, 4.7mmol, 2eq) was added followed by 1.183g of iodine (4.7mmol, 2eq) added in small portions aver 5 minutes. The mixture was warmed to room temperature over 5 minutes at which time 15mL of methylene chloride was added followed by 20mL of 10% aqueous sodium sulfite. The layers were separated and the organic layer washed with 10% sodium sulfite (3x20mL). The aqueous layer was further extracted with 20mL of methylene chloride. The combined extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated to dryness under vacuum. The crude product was chromatographed on silica gel, eluting with methylene chloride/methanol (99:1) to afford 511mg (1.68mmol, 73%) of the product. ^{1}H NMR (300MHz, $CDCl_3$): 2.70 (m,3H), 2.93 (m,1H), 4.62 (t,9Hz,1H), 6.95 (m,3H), 7.86 (br s,1H). FAB-MS: calculated for $C_{10}H_9FINO$ 305; found 306 (M+H,100%).

Step C: 3-Azido-7-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

101mg (0.33mmol) of 3-iodo-7-fluoro-2,3,4,5-tetrahydro--1H-1-benzazepin-2-one (Step B) was dissolved in 8.3mL of methylene chloride and 105mg (0.66mmol, 2eq) of tetramethylguanidinium azide was added. The mixture was stirred at room temperature for 16 hours then water was added and the layers allowed to separate. The organic layer was removed, washed with water and brine, then dried over magnesium sulfate, filtered and solvents removed under vacuum to afford 66mg (0.30mmol, 90%) of the product. ^{1}H NMR (200MHz, $CDCl_3$): 2.28 (m,1H), 2.45 (m,1H), 2.73 (m,1H), 2.93 (m,1H), 3.86 (dd;8,11Hz;1H), 7.0 (m,3H), 8.15 (br s,1H). FAB-MS:

calculated for $C_{10}H_9FN_4O$ 220; found 221 (M+H,100%).

Step D: 3-Amino-7-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

3-Azido-7-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (3.36g, 15.3mmol) (Step C) dissolved in dry tetrahydrofuran was treated with 4.00g (15.3mmol, 1eq) of triphenylphosphine and the resulting solution stirred at room temperature under nitrogen for 2 hours. Water (0.48mL, 2eq) was added and the mixture stirred at room temperature for 16 hours. Solvents were removed under vacuum and the residue purified by preparative HPLC on silica, eluting with methylene chloride/methanol (9:1) to afford 2.39g (12.3mmol, 81%) of product. ^{1}H NMR (200MHz, CD_3OD): 1.87 (m,1H), 2.41 (m,1H), 2.6-2.9 (m,2H), 3.30 (dd;8,12Hz;1H), 7.0 (m,3H). FAB-MS: calculated for $C_{10}H_{11}FN_2O$ 194; found 195 (M+H,100%).

Step E: 3-t-Butoxycarbonylamino-3-methylbutanoic acid

A solution of 4.65g (17.5mmol) of methyl 3-benzyloxycarbonylamino-3-methylbutanoate (Example 1, Step D) in 100mL absolute methanol at room temperature was treated with 3mL concentrated hydrochloric acid and hydrogenated at one atmosphere over 0.92g of 20% $Pd(OH)_2/C$. After 16 hours, an additional 0.4g of catalyst was added and hydrogenation continued for 8 hours. The catalyst was removed by filtration through Celite and the filtrate concentrated under vacuum. The residue was redissolved in 50mL methylene chloride and treated with 6.0mL (5.7g, 26mol, 1.5eq) di-t-butyl-dicarbonate followed by 7.3mL triethylamine (5.3g, 52mmol, 3eq). The mixture was stirred at room temperature for 14 hours then diluted into 300mL of hexane/ethyl acetate (1:1) and washed with water (2x), saturated aqueous sodium bicarbonate and brine. The organic layer was removed, dried over magnesium sulfate, filtered and the solvents removed under vacuum. Purification by preparative HPLC on silica, eluting with hexane/ethyl acetate (6:1), afforded 3.40g (14.7mmol, 84%) of the intermediate BOC-methyl ester as a colorless liquid.

This intermediate (3.40g, 14.7mmol) in 5mL methanol at room temperature was treated with 11mL of 2.0N NaOH (22mmol, 1.5eq) and the resulting mixture stirred at room temperature for 24 hours. The mixture was diluted with 15mL water and washed with hexane. The aqueous layer was removed, cooled to 0°, and acidified by dropwise addition of saturated aqueous potassium hydrogen sulfate to a pH of 2-3. The mixture was extracted with ethet (6x25mL); the combined extracts washed with brine, dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue solidified upon standing to afford 3.11g (14.3mmol, 97%) of the product. ^{1}H NMR (200MHz,$CDCl_3$): 1.39 (s,6H), 1.44 (s,9H), 2.72 (s,2H). FAB-MS: calculated for $C_{10}H_{19}NO_4$ 217; found 218 (M+H,54%).

Step F: 3-t-Butoxycarbonylamino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Step E) and the amine obtained in Step D by the procedure described in Example 1, Step F. ^{1}H NMR (200MHz, $CDCl_3$): 1.33 (s,6H), 1.40 (s,9H), 1.90 (m,1H), 2.45 (d,15Hz,1H), 2.56 (d,15Hz,1H), 2.60 (m,1H), 2.73 (m,1H), 2.91 (m,1H), 4.50 (m,1H), 5.16 (br s,1H), 6.66 (d,7Hz,1H), 6.94 (m,3H), 7.51 (br s,1H). FAB-MS: calculated for $C_{20}H_{28}FN_3O_4$ 393; found 394 (M+H,42%).

Step G: 3-t-Butoxycarbonylamino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]-methyl-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step F and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.34 (s,6H), 1.40 (s,9H), 1.74 (m,1H), 2.2-2.6 (m,3H), 2.43 (d,15Hz,1H), 2.53 (d,15Hz,1H), 4.43 (m,1H), 4.61 (d,14Hz,1H), 5.12 (d,14Hz,1H), 5.28 (br s,1H), 6.6-6.9 (m,3H), 6.9-7.5 (m,22H), 7.84 (m,1H).

Step H: 3-Amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

The intermediate obtained in Step G (360mg, 0.41mmol) was dissolved in 1mL of methanol and treated dropwise with 1mL of 9N HCl. The mixture was stirred at room temperature for 16 hours then all volatiles were removed under vacuum and the residue purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient; 60% methanol increased to 80% over 10 minutes) to afford 222mg

(0.35mmol, 84%) of the title compound. ^{1}H NMR (300MHz, CD_3OD): 1.39 (s,3H), 1.42 (s,3H), 2.12 (m,1H), 2.3-2.7 (m,5H), 4.40 (dd;7,12Hz;1H), 4.85 (d,15Hz,1H), 5.30 (d,15Hz,1H), 7.0-7.3 (m,6H), 7.40 (m,1H), 7.60 (m,2H), 7.70 (m,2H). FAB-MS: calculated for $C_{29}H_{30}FN_7O_2$ 527; found 528 (M+H,100%).

EXAMPLE 32

3-Amino-3-methyl-N-[8-iodo-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

Step A: 7-iodo-1-tetralone

4-(p-Iodophenyl)butyric acid (5.00g, 17.2mmol) was added to 48g of polyphosphoric acid and the mixture heated at 95°-105°C for 1 hour, then stirred at room temperature for 16 hours. The reaction mixture was added to 500mL of ice/water and extracted with ether (3x200mL). The combined extracts were dried over magnesium sulfate and the solvent removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with chloroform to yield 3.63g (13.4mmol, 77%) of the product. ^{1}H NMR (200MHz, $CDCl_3$): 2.11 (m,2H), 2.62 (t,5Hz,2H), 2.90 (t,5Hz,2H), 6.99 (d,8Hz,1H), 7.74 (dd;2,8Hz;1H), 8.30 (d,2Hz,1H). FAB-MS: calculated for $C_{10}H_9IO$ 272; found 273 (M+H,100%).

Step B: 8-iodo-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 7-iodo-1-tetralone by the procedure described in Example 31, Step A. ^{1}H NMR (200MHz, $CDCl_3$): 2.32 (m,2H), 2.42 (m,2H), 2.85 (t,6Hz,2H), 7.05 (d,8Hz,1H), 7.44 (d,2Hz,1H), 7.56 (dd;2,8Hz;1H). FAB-MS: calculated for $C_{10}H_{10}INO$ 287; found 288 (M+H,100%).

Step C: 3,8-diiodo-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 8-iodo-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step B. ^{1}H NMR (200MHz, $CDCl_3$): 2.56 (m,4H), 4.48 (t,6Hz,1H), 6.80 (d,8Hz,1H), 7.22 (d,2Hz,1H), 7.32 (dd;2,8Hz;1H). FAB-MS: calculated for $C_{10}H_9I_2NO$ 413; found 414 (M+H,58%).

Step D: 3-Azido-8-iodo-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 3,8-diiodo-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step C. ^{1}H NMR (200MHz, $CDCl_3$): 2.3-3.2 (m,4H), 3.99 (m,1H), 7.10 (d,8Hz,1H), 7.58 (m,2H). FAB-MS: calculated for $C_{10}H_9IN_4O$ 328; found 329 (M+H,100%).

Step E: 3-Amino-8-iodo-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 3-azido-8-iodo-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step D. ^{1}H NMR (200MHz, $CDCl_3$): 1.92 (m,1H), 2.56 (m,2H), 2.82 (m,1H), 3.40 (m,1H), 6.98 (d,8Hz,1H), 7.32 (d,2Hz,1H), 7.45 (dd;2,8Hz,1H), 7.60 (brs,1H). FAB-MS: calculated for $C_{10}H_{11}IN_2O$ 302; found 303 (M+H,62%).

Step F: 3-t-Butoxycarbonylamino-3-methyl-N-[8-iodo-2,3,4,5-tetrahydroahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methyl-butanoic acid (Example 31, Step E) and the amine obtained in Step E by the procedure described in Example 1, Step F. ^{1}H NMR (200MHz, $CDCl_3$): 1.33 (s,6H), 1.42 (s,9H), 1.80(m,1H), 2.24 (m,2H), 2.50 (m,3H), 4.45 (m,1H), 6.98 (d,8Hz,1H), 7.35 (d,2Hz,1H), 7.43 (dd;2,8Hz;1H). FAB-MS: calculated for $C_{20}H_{28}IN_3O_4$ 501; found 502 (M+H,20%).

Step G: 3-t-Butoxycarbonylamino-3-methyl-N-[8-iodo-2,3,4,5-tetrahydro-2-oxo-l-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]-methyl-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step F and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, CD_3OD): 1.35 (s,6H), 1.42 (s,9H), 1.70 (m,1H), 2.22 (m,2H), 2.48 (m,3H), 4.40 (m,1H), 4.39 (d,14Hz,1H), 5.28 (d,14Hz,1H), 6.74 (m,2H),

6.8-7.6 (m,23H), 7.88 (m,1H).

Step H: 3-Amino-3-methyl-N-[8-iodo-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step G by the procedure described in Example 3I, Step H. ^{1}H NMR (200MHz, CD_3OD): 1.32 (s,3H), 1.37 (s,3H), 2.04 (m,1H), 2.1-2.6 (m,3H), 2.50 (d,4Hz,2H), 4.30 (m,1H), 4.76 (d,14Hz,1H), 5.24 (d,14Hz,1H), 6.96 (m,3H), 7.15 (m,2H), 7.60 (m,6H). FAB-MS: calculated for $C_{29}H_{30}IN_7O_2$ 635; found 636 (M+H,100%).

Example 33

3-Amino-3-methyl-N-[8-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

Step A: 8-Methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 7-methoxy-I-tetralone by the procedure described in Example 31, Step A. ^{1}H NMR (200MHz, $CDCl_3$): 2.19 (m,2H), 2.32 (m,2H), 2.70 (t,6Hz,2H), 3.76 (s,3H), 6.57 (d,2Hz, 1H), 6.66 (dd;2,8Hz;1H), 7.09 (d,8Hz,1H). FAB-MS: calculated for $C_{11}H_{13}NO_2$ 191; found 192 (M+H,100%).

Step B: 3-Iodo-8-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 8-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step B. ^{1}H NMR (200MHz, $CDCl_3$): 2.6-3.1 (m,4H), 3.88 (s,3H), 4.76 (t,6Hz,1H), 6.68 (d,2Hz,1H), 6.81 (dd;2,8Hz;1H), 7.20 (d,2Hz,1H). FAB-MS: calculated for $C_{11}H_{12}INO_2$ 317; found 318 (M+H,44%).

Step C: 3-Azido-8-methoxy-2,3,4,5-tetrahydro-1H-1-benzazpin-2-one

Prepared from 3-iodo-8-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step C. ^{1}H NMR (200MHz, $CDCl_3$): 2.3-3.2 (m,4H), 3.90 (s,3H), 4.01 (m,1H), 6.74 (d,2Hz,1H), 6.82 (dd;2,8Hz;1H), 7.22 (d,8Hz,1H). FAB-MS: calculated for $C_{11}H_{12}N_4O_2$ 232; found 233 (M+H,100%).

Step D: 3-Amino-8-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 3-azido-8-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step D. ^{1}H NMR (200MHz, $CDCl_3$): 2.02 (m,1H), 2.68 (m,2H), 2.90 (m,1H), 3.59 (m,1H), 3.92 (s,3H), 6.74 (d,2Hz,1H), 6.82 (dd;2,8Hz;1H), 7.22 (d,8Hz,1H), 8.25 (br s,1H). FAB-MS: calculated for $C_{11}H_{14}N_2O_2$ 206; found 207 (M+H,40%).

Step E: 3-t-Butoxycarbonylamino-3-methyl-N-[8-methoxy-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and the amine obtained in Step D by the procedure described in Example 1, Step F. ^{1}H NMR (200MHz, $CDCl_3$): 1.44 (s,6H), 1.50 (s,9H), 1.80 (m,1H), 2.80 (m,5H), 3.86 (s,3H), 4.62 (m,1H), 6.62 (d,2Hz,1H), 6.76 (dd;2,8Hz;1H), 7.20 (d,8Hz,1H). FAB-MS: calculated for $C_{21}H_{31}N_3O_5$ 405; found 406 (M+H,42%).

Step F: 3-t-Butoxycarbonylamino-3-methyl-N-[8-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step E and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K.^{1}H NMR (200MHz, CD_3OD): 1.47 (s,6H), 1.55 (s,9H), 1.80 (m,1H), 2.42 (m,2H), 2.60 (m,3H), 3.84 (s,3H), 4.62 (m,1H), 4.78 (d,14Hz,1H), 5.30 (d,14Hz,1H), 6.79 (m,2H), 7.08 (m,12H), 7.42 (m,11H), 7.98 (m,1H).

Step G: 3-t-Butoxycarbonylamino-3-methyl-N-[8-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step F by the procedure described in Example 2, Step C. ^{1}H NMR (200MHz, CD_3OD): 1.42 (s,6H), 1.50 (s,9H), 2.10 (m,1H), 2.56 (m,5H), 3.82 (s,3H), 4.43 (m,1H), 4.92 (d,15Hz,1H), 5.31 (d,15Hz,1H), 6.86 (m,1H), 6.97 (m,2H), 7.0-7.3 (m,4H), 7.64 (m,3H), 8.05 (m,1H), FAB-MS: calculated for $C_{35}H_{41}N_7O_5$ 639; found 640 (M+H,20%).

Step H: 3-Amino-3-methyl-N-[8-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]butanamide, mono(trifluoacetate)

The title compound was prepared from the intermediate obtained in Step G by the procedure described in Example 31, Step H. ^{1}H NMR (200MHz, CD_3OD): 1.43 (s,3H), 1.49 (s,3H), 2.15 (m,1H), 2.2-2.7 (m,5H), 3.85 (s,3H), 4.48 (m,1H), 5.04 (d,14Hz,1H), 5.28 (d,14Hz,1H), 6.92 (m,2H), 7.1-7.4 (m,4H), 7.65 (m,5H). FAB-MS: calculated for $C_{30}H_{33}N_7O_3$ 539; found 540 (M+H,100%).

Example 34

3-Amino-3-methyl-N-[7-trifluoromethyl-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, hydrochloride

Step A: 3-(Trifluoromethyl)phenethyl tosylate

A solution of 10.0g (52.6mmol) of 3-(trifluoromethyl)phenethyl alcohol in 75mL of ether under nitrogen was treated with 10.53g (55.2mmol, 1.05eq) p-toluenesulfonyl chloride. The solution was cooled to 0° and treated with 7.67mL (5.57g, 55.0mmol, 1.05eq) of triethylamine. The mixture was stirred at 0° for 30 minutes then warmed to room temperature and stirred for 16 hours. The precipitate was removed by filtration and washed with ether. The combined filtrate and ether wash were evaporated under vacuum. The residue was redissolved in ethyl acetate and washed with 0.5N HCl and brine; the organic layer was removed, dried over sodium sulfate, filtered and concentrated under vacuum. Purification by flash chromatography on silica, eluting with 30% ethyl acetate/hexane, afforded 15.14g (44.0mmol, 84%) of the product. ^{1}H NMR (200MHz, $CDCl_3$): 2.44 (s,3H), 3.03 (t,7Hz,2H), 4.26 (t,7Hz,2H), 7.2-7.5 (m,6H), 7.66 (d,8Hz,2H). FAB-MS: calculated for $C_{16}H_{15}F_3SO_3$ 344; found 345 (M+H, 8%).

Step B: 2-[2-(3-Trifluoromethylphenyl)-ethyl]propane-1,3-dioic acid, dimethyl ester

A suspension of 1.4g of 60% sodium hydride oil dispersion (0.84g, 35mmol, 1.1eq) in 30mL of tetrahydrofuran at room temperature under nitrogen was treated dropwise over 15 minutes with a solution of 4.0mL of dimethyl malonate (4.62g, 35mmol, 1.1eq) in 30mL of tetrahydrofuran. After evolution of hydrogen ceased, a solution of 11.03g (32.0mmol, 1.0eq) of 3-(trifluoromethyl)phenethyl tosylate (Step A) in 30mL of tetrahydrofuran was added over 15 minutes. The mixture was heated at reflux for a total of 21 hours. The mixture was filtered; the filtrate was dried over magnesium sulfate, filtered and concentrated under vacuum to afford 10.89g of product which contained approximately 5% of unreacted tosylate and was used without purification. ^{1}H NMR (200MHz, $CDCl_3$): 2.24 (m,2H), 2.70 (t,8Hz,2H), 3.37 (t,8Hz,1H), 3.74 (s,6H), 7.3-7.5 (m,4H).

Step C: 4-(3-Trifluoromethylphenyl)-butanoic acid

The intermediate obtained in Step B (2.15g, 7.07mmol) was treated with 3.5mL of a 4.53M solution of methanolic potassium hydroxide (15.9mmol, 2.2eq) and the resulting mixture stirred at room temperature for 72 hours. The mixture was concentrated under vacuum and the solid residue redissolved in 4mL of concentrated hydrochloric acid and heated at reflux for 3 hours. The mixture was cooled, then extracted with methylene chloride (3x6mL); the combined extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was suspended in 20mL of water and treated with 700mg (8.3mmol) of sodium bicarbonate. The solution was washed with ether (2x20mL); the aqueous phase was removed and acidified (pH 1-2) with 2N HCl. The mixture was extracted with methylene chloride and the combined extracts dried over sodium sulfate, filtered and concentrated under vacuum. The residue was treated with 30mL of concentrated hydrochloric acid and the mixture heated at reflux for 20 hours. All volatiles were removed under vacuum to afford 1.12g (4.82mmol, 68%) of product. ^{1}H NMR (200MHz, $CDCl_3$): 1.98 (m,2H), 2.40 (t,8Hz,2H), 2.74

(t,8Hz,2H), 7.3-7.5 (m,4H).

Step D: 7-Trifluoromethyl-1-tetralone

Prepared from 4-(3-trifluoromethylphenyl)butanoic acid by the procedure described in Example 32, Step A. ^{1}H NMR (200MHz, $CDCl_3$): 2.16 (m,2H), 2.69 (t,6Hz,2H), 3.01 (t,6Hz,2H), 7.5 (m,2H), 8.12 (d,8Hz,1H). EI-MS: calculated for $C_{11}H_9F_3O$ 214; found 214 (M^+,40%).

Step E: 7-Trifluoromethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 7-trifluoromethyl-1-tetralone by the procedure described in Example 31, Step A. ^{1}H NMR (200MHz, $CDCl_3$): 2.3 (m,4H), 2.86 (t,7Hz,2H), 7.08 (d,8Hz,1H), 7.48 (m,2H), 8.3 (br s,1H).
FAB-MS: calculated for $C_{11}H_{10}F_3NO$ 229; found 230 (M+H,100%).

Step F: 3-Iodo-7-trifluoromethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 7-trifluoromethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step B. ^{1}H NMR (200MHz, $CDCl_3$): 2.8 (m,4H), 4.68 (t,8Hz,1H), 7.11 (d,8Hz,1H), 7.52 (m,2H), 7.95 (br s,1H). FAB-MS: calculated for $C_{11}H_9F_3INO$ 355; found 356 (M+H,100%).

Step G: 3-Azido-7-trifluoromethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 3-iodo-7-trifluoromethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step C. ^{1}H NMR (200MHz, $CDCl_3$): 2.32 (m,1H), 2.55 (m,1H), 2.81 (m,1H), 3.00 (m,1H), 3.88 (dd;8,12Hz;1H), 7.14 (d,7Hz,1H), 7.52 (m,2H), 8.34 (br s,1H). FAB-MS: calculated for $C_{11}H_9F_3N_4O$ 270; found 271 (M+H,100%).

Step H: 3-Amino-7-trifluoromethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 3-azido-7-trifluoromethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step D. ^{1}H NMR (200MHz, CD_3OD): 1.95 (m,1H), 2.46 (m,1H), 2.80 (m,2H), 3.35 (dd;8,12Hz;1H), 7.15 (d,8Hz,1H), 7.63 (m,2H). FAB-MS: calculated for $C_{11}H_{11}F_3N_2O$ 244; found 245 (M+H,100%).

Step I: 3-t-Butoxycarbonylamino-3-methyl-N-[7-trifluoromethyl-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and the amine obtained in Step H by the procedure described in Example 1, Step F. ^{1}H NMR (200MHz, $CDCl_3$): 1.34 (s,6H), 1.42 (s,9H), 1.98 (m,1H), 2.50 (d,14Hz,1H), 2.63 (d,14Hz,1H), 2.7-3.0 (m,3H), 4.50 (m,1H), 6.75 (d,7Hz,1H), 7.10 (d,8Hz,1H), 7.51 (br s,2H), 7.94 (br s,1H). FAB-MS: calculated for $C_{21}H_{28}F_3N_3O_4$ 443; found 444 (M+H,74%).

Step J: 3-t-Butoxycarbonylamino-3-methyl-N-[7-trifluoromethyl-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3-yl]butanamide

Prepared from the intermediate obtained in Step I and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.36 (s,6H), 1.42 (s,9H), 1.71 (m,1H), 2.4-2.6 (m,5H), 4.44 (m,1H), 4.75 (d,15Hz,1H), 5.11 (d,15Hz,1H), 5.19 (br s,1H), 6.64 (d,7Hz,1H), 6.9-7.1 (m,10H), 7.2-7.5 (m,15H), 7.88 (m,1H).

Step K: 3-amino-3-methyl-N-[7-trifluoromethyl-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, hydrochloride

The intermediate prepared in Step J (436mg, 0.47mmol) was dissolved in 4mL of methanol and treated dropwise with 4mL of 9N HCl. The mixture was stirred at room temperature for 16 hours then evaporated to dryness under vacuum. The dry solid was triturated with benzene (5x5mL) then with warm benzene (2x5mL) then dried to constant weight. Thus, 304mg (0.47mmol, 100%) of the title compound was obtained. ^{1}H NMR

(200MHz, CD_3OD): 1.33 (s,3H), 1.36 (s,3H), 2.1-2.8 (m,6H), 4.30 (dd;8,12Hz;1H), 4.96 (d,15Hz,1H), 5.33 (d,15Hz,1H), 7.06 (d,8Hz,2H), 7.2-7.5 (m,3H), 7.5-7.7 (m,6H). FAB-MS: calculated for $C_{30}H_{30}F_3N_7O_2$ 577; found 578 (M+H,100%).

Example 35

3-amino-3-methyl-N-[8-chloro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

Step A: 7-Amino-1-tetralone

7-Nitrotetralone (2.5g, 13mmol) was suspended in 50mL of methanol and complete dissolution achieved by the addition of 10mL of tetrahydrofuran. The solution was hydrogenated at room temperature and 20-30psi over 100mg of 10% Pd/C for 2 hours. The mixture was filtered through Celite, washed with methanol and evaporated to dryness under vacuum to afford 2.1g (13mmol, 100%) of the product. ^1H NMR (300MHz, $CDCl_3$): 2.09 (m,2H), 2.60 (t,6Hz,2H), 2.84 (t,6Hz,2H), 6.83 (m,1H), 7.06 (d,8Hz,1H), 7.32 (d,2Hz,1H). FAB-MS: calculated for $C_{10}H_{11}NO$ 161; found 162 (M+H,100%).

Step B: 7-chloro-1-tetralone

7-Amino-1-tetralone (500mg, 3.1mmol) was suspended in 3mL of water and treated with 3mL of concentrated hydrochloric acid with stirring. The mixture was cooled in an ice bath and treated dropwise with vigorous stirring with a solution of 241mg of sodium nitrite in 1.5mL of water (3.5mmol, 1.1eq). The mixture was stirred at 0-5° for 15 minutes then added dropwise to a cold solution of 366mg of CuCl (3.7mmol, 1.2eq) in 6mL of concentrated hydrochloric acid. The mixture was stirred for 5 minutes at 0° and 1 hour at room temperature. The mixture was extracted with methylene chloride (3x15mL); the combined extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated to dryness under vacuum at room temperature to give 550mg (3.05mmol, 98%) of the product. ^1H NMR (300MHz, $CDCl_3$): 2.16 (m,2H), 2.67 (t,6Hz,2H), 2.95 (t,6Hz,2H), 7.22 (d,8Hz,1H), 7.44 (dd;2,8Hz;1H), 8.01 (d,2Hz,1H). FAB-MS: calculated for $C_{10}H_9ClO$ 180; found 181 (M+H,10%).

Step C: 8-Chloro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 7-chloro-1-tetralone by the procedure described in Example 31, Step A. ^1H NMR (300MHz, $CDCl_3$): 2.23 (m,2H), 2.37 (t,6Hz,2H), 2.80 (t,6Hz,2H), 7.1 (m,3H), 9.08 (br s,1H). FAB-MS: calculated for $C_{10}H_{10}ClNO$ 195; found 195 (M^+,30%).

Step D: 3-Iodo-8-chloro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step C by the procedure described in Example 31, Step B. ^1H NMR (300MHz, $CDCl_3$): 2.72 (m,3H), 2.90 (m,1H), 4.67 (t,8Hz,1H), 7.05 (s,1H), 7.18 (s,2H), 7.71 (br s,1H). FAB-MS: calculated for $C_{10}H_9ClINO$ 320; found 321 (M+H,100%).

Step E: 3-Azido-8-chloro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step D by the procedure described in Example 31, Step C. ^1H NMR (300MHz, DMF-d_7): 2.10 (m,1H), 2.40 (m,1H), 2.76 (m,2H), 4.01 (dd;8,12Hz;1H), 7.10 (d,2Hz,1H), 7.16 (dd;2,8Hz;1H), 7.30 (d,8Hz,1H), 7.95 (br s,1H). FAB-MS: calculated for $C_{10}H_9ClN_4O$ 236; found 237 (M+H,100%).

Step F: 3-Amino-8-chloro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step E by the procedure described in Example 31, Step D. ^1H NMR (300MHz, $CDCl_3$): 1.94 (m,1H), 2.52 (m,1H), 2.67 (m,1H), 2.89 (m,1H), 3.44 (m,1H), 7.02 (d,2Hz,1H), 7.18 (m,2), 7.70 (br s,2H). FAB-MS: calculated for $C_{10}H_{11}ClN_2O$ 210; found 211 (M+H,84%).

Step G: 3-t-Butoxycarbonylamino-3-methyl-N-[8-chloro-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and the amine obtained in Step F by the procedure described in Example 1, Step F. ^{1}H NMR (300MHz, $CDCl_3$): 1.35 (s,6H), 1.42 (s,9H), 1.95 (m,1H), 2.4-2.8 (m,5H), 4.51 (m,1H), 5.22 (br s,1H), 6.73 (d,7Hz,1H), 7.02 (s,1H), 7.14 (br s,2H), 8.21 (br s,1H). FAB-MS: calculated for $C_{20}H_{28}ClN_3O_4$ 409; found 410 (M+H,55%).

Step H: 3-t-Butoxycarbonylamino-3-methyl-N-[8-chloro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step G and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K.

Step I: 3-Amino-3-methyl-N-[8-chloro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]butanamide, trifluoroacetate

Prepared from the intermediate obtained in Step H by the procedure described in Example 31, Step H. ^{1}H NMR (300MHz, CD_3OD): 1.40 (s,3H), 1.43 (s,3H), 2.12 (m,1H), 2.3-2.7 (m,5H), 4.30 (dd;8,12Hz;1H), 4.87 (d,15Hz,1H), 5.34 (d,15Hz,1H), 7.08 (d,8Hz,2H), 7.23 (d,8Hz,2H), 7.28 (s,2H), 7.45 (s,1H), 7.59 (t,8Hz,2H), 7.70 (m,2H). FAB-MS calculated for $C_{29}H_{30}ClN_7O_2$ 543; found 544 (M+H,43%).

Example 36

3-Amino-3-methyl-N-[8-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

Step A: 7-Fluoro-1-tetralone

In a specially designed Kel-F reactor (cylindrical shape 1.25"od x 3"h equipped with a screw cap and N_2 inlet-outlet) was placed hydrogen fluoride-pyridine 6:4 solution (10mL, prepared by diluting commercially available hydrogen fluoride-pyridine 7:3 solution with dry pyridine). 7-amino-tetralone (644mg, 4.0mmol), (Example 35, Step A) was added under N_2 and the solution was cooled to 0°. Sodium nitrite (304mg, 4.4mol, 1.1eq) was added in portions and the mixture was stirred for 30 minutes. The mixture was then heated at 90°C for 1 hour with stirring. The reaction mixture was quenched with approx. 60mL of ice/water and the solid that separated extracted with methylene chloride (3x30mL). The combined extracts were washed with water and brine, dried over magnesium sulfate, filtered and evaporated to dryness under vacuum at room temperature. Purification by flash chromatography on silica, eluting with ethyl acetate/hexane (5:95), afforded pure 7-fluoro-1-tetralone (367mg, 2.2mmol, 56%). ^{1}H NMR (300MHz, $CDCl_3$): 2.13 (m,2H), 2.65 (t,7Hz,2H), 2.94 (t,7Hz,2H), 7.1-7.3 (m,2H), 7.69 (dd;2,8Hz;1H). EI-MS: calculated for $C_{10}H_9FO$ 164; found 164 (M^+,71%).

Step B: 8-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 7-fluoro-1-tetralone by the procedure described in Example 31, Step A. ^{1}H NMR (300MHz, $CDCl_3$): 2.22 (m,2H), 2.38 (t,6Hz,2H), 2.78 (t,6Hz,2H), 6.75 (dd;2,8Hz;1H), 6.84 (dt;2,8Hz;1H), 7.16 (t,8Hz,1H), 8.35 (br s,1H).

Step C: 3-Iodo-8-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step B by the procedure described in Example 31, Step B. ^{1}H NMR (300MHz, $CDCl_3$): 2.73 (m,3H), 2.92 (m,1H), 4.68 (t,8Hz,1H), 6.79 (dd;2,8Hz;1H), 6.90 (dt;2,8Hz;1H), 7.18 (t,8Hz,1H), 8.14 (br s,1H).

Step D: 3-Azido-8-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step C by the procedure described in Example 31, Step C. ^{1}H NMR (300MHz, $CDCl_3$): 2.30 (m,1H), 2.51 (m,1H), 2.74 (m,1H), 2.93 (m,1H), 3.88 (dd;8,12Hz;1H), 6.80 (dd;2,8Hz;1H), 6.89 (dt;2,8Hz;1H), 7.21 (t,8Hz,1H), 8.10 (br s,1H).

Step E: 3-Amino-8-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step D by the procedure described in Example 31, Step D. ^{1}H NMR (300MHz, $CDCl_3$): 1.92 (m,1H), 2.52 (m,1H), 2.65 (m,1H), 2.86 (m,1H), 3.45 (m,1H), 6.78 (dd;2,8Hz;1H), 6.87 (dt;2,8Hz;1H), 7.20 (t,8Hz,1H), 8.56 (br s,1H). FAB-MS: calculated for $C_{10}H_{11}FN_2O$ 194; found 195 (M+H,100%).

Step F: 3-t-Butoxycarbonylamino-3-methyl-N-[8-fluoro-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and the amine obtained in Step E by the procedure described in Example 1, Step F. ^{1}H NMR (300MHz, $CDCl_3$): 1.35 (s,6H), 1.41 (s,9H), 1.93 (m,1H), 2.4-2.9 (m,5H), 4.54 (m,1H), 5.19 (br s,1H), 6.73 (m,2H), 6.88 (dt;2,8Hz;1H), 7.19 (dd;6,8Hz;1H), 8.07 (m,1H). FAB-MS: calculated for $C_{20}H_{28}FN_3O_4$ 393; found 394 (M+H,56%).

Step G: 3-t-Butoxycarbonylamino-3-methyl-N-[8-fluoro2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step F and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (300MHz, $CDCl_3$): 1.36 (s,3H), 1.37 (s,3H), 1.42 (s,9H), 1.75 (m,1H), 2.3-2.6 (m,5H), 4.5 (m,2H), 5.25 (m,2H), 6.64 (d,7Hz,1H), 6.8-7.I (m,11H), 7.2-7.5 (m,13H), 7.85 (m,1H).

Step H: 3-Amino-3-methyl-N-[8-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]butanamide trifluoroacetate

Prepared from the intermediate obtained in Step G by the procedure described in Example 31, Step H. ^{1}H NMR (300MHz, CD_3OD): 1.40 (s,3H), 1.43 (s,3H), 2.12 (m,1H), 2.3-2.7 (m,5H), 4.41 (dd;8,12Hz;1H), 4.88 (d,15Hz,1H), 5.34 (d,15Hz,1H), 7.0-7.2 (m,3H), 7.2-7.4 (m,5H), 7.5-7.8 (m,3H). FAB-MS: calculated for $C_{29}H_{30}FN_7O_2$ 527; found 528 (M+H,100%).

Example 37

3-Amino-3-methyl-N-(6-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

Step A: 4-(2-Fluorophenyl)butyric acid

Prepared from 4-(2-aminophenyl)butyric acid by the procedure described in Example 36, Step A. ^{1}H NMR (300MHz, $CDCl_3$): 1.95 (m,2H), 2.39 (t,7Hz,2H), 2.70 (t,7Hz,2H), 6.9-7.3 (m,4H). FAB-MS: calculated for $C_{10}H_{11}FO_2$ 182; found 182 (M^+,75%).

Step B: 5-Fluoro-1-tetralone

Prepared from 4-(2-fluorophenyl)butyric acid by the procedure described in Example 32, Step A. ^{1}H NMR (300MHz, $CDCl_3$): 2.10 (m,2H), 2.60 (t,7Hz,2H), 2.88 (t,7Hz,2H), 7.1-7.3 (m,2H), 7.78 (d,8Hz,1H). EI-MS: calculated for $C_{10}H_9FO$ 164; found 164 (M^+,44%).

Step C: 6-Fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 5-fluoro-1-tetralone by the procedure described in Example 31, Step A. ^{1}H NMR (300MHz, $CDCl_3$): 2.26 (m,2H), 2.40 (t,6Hz,2H), 2.88 (t,6Hz,2H), 6.83 (d,8Hz,1H), 6.94 (t,8Hz,1H), 7.20 (m,1H), 7.75 (br s,1H). FAB-MS: calculated for $C_{10}H_{10}FNO$ 179; found 180 (M+H,100%).

Step D: 3-Iodo-6-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step C by the procedure described in Example 31, Step B. ^{1}H NMR (300MHz, $CDCl_3$): 2.7-2.9 (m,3H), 2.97 (m,1H), 4.68 (t,8Hz,1H), 6.81 (d,8Hz,1H), 6.94 (t,8Hz,1H), 7.20

(m,1H), 7.83 (br s,1H).

Step E: 3-Azido-6-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step D by the procedure described in Example 31, Step C. ^{1}H NMR (200MHz, $CDCl_3$): 2.2-2.8 (m,4H), 3.88 (dd;8,12Hz;1H), 6.85 (d,8Hz,1H), 6.95 (t,8Hz,1H), 7.22 (m,1H), 7.27 (br s,1H).

Step F: 3-Amino-6-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step E by the procedure described in Example 31, Step D. ^{1}H NMR (300MHz, CD_3OD): 2.22 (m,1H), 2.60 (m,2H), 3.21 (m,1H), 3.85 (dd;8,12Hz;1H), 6.91 (d,8Hz,1H), 7.02 (t,8Hz,1H), 7.30 (m,1H). FAB-MS: calculated for $C_{10}H_{11}FN_2O$ 194; found 195 (M+H,100%).

Step G: 3-t-Butoxycarbonylamino-3-methyl-N-[6-fluoro-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and the amine obtained in Step F by the procedure described in Example 1, Step F. ^{1}H NMR (300MHz, $CDCl_3$): 1.36 (s,6H), 1.43 (s,9H), 1.91 (m,1H), 2.4-2.8 (m,3H), 3.18 (m,2H), 4.54 (m,1H), 5.18 (br s,1H), 6.66 (d,7Hz,1H), 6.81 (d,8Hz,1H), 6.94 (t,8Hz,1H), 7.18 (m,1H), 7.71 (br s,1H). FAB-MS: calculated for $C_{20}H_{28}FN_3O_4$ 393; found 394 (M+H,26%).

Step H: 3-t-Butoxycarbonylamino-3-methyl-N-[6-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(N-triphenylmethyl)-tetrazol-5-yl][1,1′-biphenyl]-4-yl]methyl-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step G and N-triphenylmethyl-5-[2-(4′-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (300MHz, $CDCl_3$): 1.38 (s,6H), 1.45 (s,9H), 1.81 (m,1H), 2.18 (m,1H), 2.4-2.7 (m,3H), 2.89 (dd;7,14Hz;1H), 4.52 (m,1H), 4.77 (d,15Hz,1H), 5.09 (d,15Hz,1H), 5.29 (br s,1H), 6.67 (d,7Hz,1H), 6.9-7.2 (m,12H), 7.2-7.5 (m,13H), 7.85 (m,1H).

Step I: 3-Amino-3-methyl-N-[6-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]butanamide, trifluoroacetate

Prepared from the intermediate obtained in Step H by the procedure described in Example 31, Step H. ^{1}H NMR (300MHz, CD_3OD): 1.32 (s,3H), 1.36 (s,3H), 2.0-2.3 (m,3H), 2.40 (br s,2H), 3.00 (m,1H), 4.35 (m,1H), 4.87 (d,15Hz,1H), 5.20 (d,15Hz,1H), 7.00 (m,3H), 7.1-7.4 (m,4H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{29}H_{30}FN_7O_2$ 527; found 528 (M+H,100%).

EXAMPLE 38

3-Amino-3-methyl-N-[1,2,3,4,5,6-hexahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]1H-1-benzazocin-3-yl]-butanamide, trifluoroacetate

Step A: 3-benzyloxycarbonylamino-3-methyl-N-[1,2,3,4,5,6-hexahydro-2-oxo-1H-1-benzazocin-3-yl]butanamide

3-Azido-3,4,5,6-tetrahydro-1-benzazocin-2(1H)-one prepared by the method of Watthey, et al., J. Med. Chem., 28, 1511-1516 (1985)) was reduced to 3-amino-3,4,5,6-tetrahydro-1-benzazocin-2(1H)-one by the procedure described in Example 1, Step A, then coupled with 3-benzyloxycarbonylamino-3-methylbutanoic acid (Example 1, Step E) by the procedure described in Example 1, Step F. ^{1}H NMR (200MHz, $CDCl_3$): 1.36 (s,6H), 1.75 (m,3H), 2.08 (m,1H), 2.47 (m,3H), 2.80(m,1H), 4.13 (m,1H), 5.12 (s,2H), 5.79 (s,1H), 6.86 (d,7Hz,1H), 7.0-7.4 (m,8H), 7.90 (s,1H). FAB-MS: calculated for $C_{24}H_{29}N_3O_4$ 423; found 424 (M+H,100%).

Step B: 3-Benzyloxycarbonylamino-3-methyl-N-[1,2,3,4,5,6-hexahydro-2-oxo-1-[[2′-(N-triphenylmethyl)-tetrazol-5-yl][1,1′-biphenyl]-4-yl]methyl-1H-1-benzazocin-3-yl]-butanamide

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4′-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.42 (s,6H), 1.72

(m,4H), 2.42 (m,4H), 4.16 (m,1H), 4.49 (d,13Hz,1H), 5.10 (s,2H), 5.30 (d,13Hz,1H), 5.79 (s,1H), 6.80 (d,6Hz,2H), 6.9-7.6 (m,32H), 7.86 (m,1H).

Step C: 3-Amino-3-methyl-N-[1,2,3,4,5,6-hexahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]-1H-1-benzazocin-3-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 1, Step L. ^{1}H NMR (200MHz, CD_3OD): 1.28 (s,3H), 1.32 (s,3H), 1.44 (m,1H), 1.75 (m,3H), 2.05 (m,1H), 2.48 (m,3H), 4.00 (m,1H), 4.64 (d,13Hz,1H), 5.19 (d,13Hz,1H), 6.9-7.4 (m,8H), 7.4-7.7 (m,4H). FAB-MS: calculated for $C_{30}H_{33}N_7O_2$ 523; found 524 (M+H,100%).

Example 39

3-Amino-3-methyl-N-[1,2,3,4-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-quinolin-3-yl]-butanamide, trifluoroacetate

Step A: 3-Benzyloxycarbonylamino-3-methyl-N-[1,2,3,4-tetrahydro-2-oxo-1H-1-quinolin-3-yl]-butanamide

Prepared as in Example 1, Step F from 3-amino-1,2,3,4-tetrahydroquinolin-2-one (prepared by the method of Davis, et al; Arch. Biochem. Biophys., 102, 48 (1963)) and 3-benzyloxycarbonylamino-3-methylbutanoic acid (Example 1, Step E). ^{1}H NMR (200MHz, $CDCl_3$): 1.42 (s,6H), 2.68 (s,2H), 2.86 (t,13Hz,1H), 3.00 (m,1H), 4.67 (m,1H), 5.00 (s,2H), 6.9-7.3 (m,9H). FAB-MS: calculated for $C_{22}H_{25}N_3O_4$ 395; found 396 (M+1,100%).

Step B: 3-Benzyloxycarbonylamino-3-methyl-N-[1,2,3,4-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-quinolin-3-yl]-butanamide

Prepared from 3-benzyloxycarbonylamino-3-methyl-N-[1,2,3,4-tetrahydro-2-oxo-1H-1-quinolin-3-yl]-butanamide and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, CD_3OD): 1.41 (s,6H), 2.66 (s,2H), 2.85 (t,11Hz,1H), 3.11 (m,1H), 4.15 (m,1H), 4.97 (d,15Hz,1H), 5.30 (d,15Hz,1H), 6.7-7.6, (m,26H), 7.80 (m,1H).

Step C; 3-Amino-3-methyl-N-[1,2,3,4-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-quinolin-3-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 1, Step L. ^{1}H NMR (200MHz, CD_3OD): 1.50 (s,3H), 1.52 (s,3H), 2.66 (m,2H), 3.16 (m,2H), 4.84 (m,1H), 5.17 (d,11Hz,1H), 5.39 (d,11Hz,1H), 7.0-7.4 (m,8H), 7.57 (m,4H). FAB-MS: calculated for $C_{28}H_{29}N_7O_2$ 495; found 496 (M+H,100%).

Example 40

3-Benzylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1benzazepin-3(R)-yl]-butanamide trifluoroacetate(Example I) and benzaldehyde by the procedure described in Example 18. ^{1}H NMR (200MHz, CD_3OD): 1.42 (s,3H), 1.46 (s,3H), 2.0-2.6 (m,4H), 2.69 (br s,2H), 4.12 (s,2H), 4.37 (dd;8,12Hz;1H), 4.90 (d,15Hz,1H), 5.18 (d,15Hz,1H), 6.97 (d,8Hz,2H), 7.1-7.7 (m,15H). FAB-MS: calculated for $C_{36}H_{37}N_7O_2$ 599; found 600 (M+H,100%).

Example 41

3-Isobutylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide trifluoroacetate (Example 1) and isobutyraldehyde by the procedure described in Example 18. ^{1}H NMR (200MHz, CD_3OD): 0.99 (d,8Hz,3H), 1.00

(d,8Hz,3H), 1.35 (s,3H), 1.39 (s,3H), 1.8-2.6 (m,7H), 2.81 (d,7Hz,2H), 4.32 (dd;8,12Hz;1H), 4.92 (d,15Hz,1H), 5.14 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.1-7.4 (m,6H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{33}H_{39}N_7O_2$ 565; found 566 (M+H,100%).

Example 42

3-Propylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide trifluoroacetate (Example 1) and propionaldehyde by the procedure described in Example 18. ^{1}H NMR (200MHz, CD_3OD): 0.97 (t,8Hz,3H), 1.32 (s,3H), 1.36 (s,3H), 1.65 (m,2H), 2.0-2.6 (m,8H), 2.93 (t,7Hz,2H), 4.33 (dd;7,11Hz;1H), 4.89 (d,15Hz,1H), 5.18 (d,15Hz,1H), 6.99 (d,8Hz,2H), 7.10-7.35 (m,6H), 7.45-7.65 (m,4H). FAB-MS: calculated for $C_{32}H_{37}N_7O_2$ 551; found 552 (M+H,73%).

Example 43

3-(Cyclopropylmethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide trifluoroacetate (Example 1) and cyclopropanecarboxaldehyde by the procedure described in Example 18. ^{1}H NMR (200MHz, CD_3OD): 0.37 (m,2H), 0.65 (m,2H), 1.00 (m,1H), 1.34 (s,3H), 1.36 (s,3H), 2.0-2.6 (m,6H), 2.88 (d,7Hz,2H), 4.33 (dd;7,11Hz;1H), 4.89 (d,15Hz,1H), 5.18 (d,15Hz,1H), 7.01 (d,8Hz,2H), 7.15-7.35 (m,6H), 7.45-7.70 (m,4H). FAB-MS: calculated for $C_{33}H_{37}N_7O_2$ 563; found 564 (M+H,100%).

Example 44

3-(Cyclohexylmethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide trifluoroacetate (Example 1) and cyclohexanecarboxaldehyde by the procedure described in Example 18. ^{1}H NMR (200MHz, CD_3OD): 0.8-1.4 (m,6H), 1.33 (s,3H), 1.37 (s,3H), 1.5-1.9 (m,5H), 2.0-2.6 (m,6H), 2.80 (d,7Hz,2H), 4.32 (dd;8,12Hz;1H), 4.92 (d,15Hz,1H), 5.14 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.10-7.35 (m,6H), 7.45-7.70 (m,4H). FAB-MS: calculated for $C_{36}H_{43}N_7O_2$ 605; found 606 (M+H,100%).

Example 45

3-(4-hydroxybenzyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 3-(4-benzyloxybenzyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1Htetrazol-5-yl)-[1,1-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide trifluoroacetate (Example 1) and 4-benzyloxybenzaldehyde by the procedure described in Example 18. ^{1}H NMR (200MHz, CD_3OD): 1.32 (s,3H), 1.35 (s,3H), 2.0-2.7 (m,6H), 4.10 (s,2H), 4.36 (dd;8,12Hz;1H), 4.91 (d,15Hz,1H), 5.02 (s,2H), 5.09 (d,15Hz,1H), 6.98 (d,8Hz,6H), 7.1-7.6 (m,15H). FAB-MS: calculated for $C_{43}H_{43}N_7O_3$ 705; found 706 (M+H,100%).

Step B: 3-(4-Hydroxybenzyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The intermediate obtained in Step A (14.6mg, 0.018mmol) dissolved in 1.5mL of methanol was hydrogen-

ated at room temperature and one atmosphere over 10mg of 10% Pd/C for 2 hours. The reaction mixture was filtered through Celite and the filtrate concentrated under vacuum. The residue was purified by reverse phase HPLC on C-18 eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 75% methanol over 10 minutes) to afford 8.1mg (0.011mmol, 62%) of the title compound. ^{1}H NMR (200MHz, CD_3OD): 1.40 (s,3H), 1.44 (s,3H), 2.0-2.7 (m,6H), 4.08 (s,2H), 4.36 (m,1H), 4.87 (d,15Hz,1H), 5.20 (d,15Hz,1H), 6.78 (d,8Hz,2H), 6.96 (d,8Hz,2H), 7.1-7.7 (m,12H). FAB-MS: calculated for $C_{36}H_{37}N_7O_3$ 615; found 616 (M+H,46%).

Example 46

3-Amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, trifluoroacetate

Step A: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-4-oxo-1,5-benzothiazepin-3(S)-yl]butanamide

Prepared from 3(S)-amino-3,4-dihydro-1,5-benzothiazepin-4(5H)-one (prepared from D-cysteine (S-cysteine) by the method of Slade, et al, J. Med. Chem., 28, 1517-1521 (1985)) and 3-t-butoxycarbonyl-amino-3-methylbutanoic acid (Example 31, Step E) by the procedure described in Example 1, Step F. ^{1}H NMR (200MHz, $CDCl_3$): 1.38 (s,6H), 1.45 (s,9H), 2.32 (d,10Hz,1H), 2.50 (d,14Hz,1H), 2.70 (d,14Hz,1H), 2.92 (t,11Hz,1H), 3.93 (dd;7,11Hz;1H), 4.76 (m,1H), 7.02 (d,8Hz,1H), 7.1-7.3 (m,2H), 7.40 (t,8Hz,1H), 7.66 (d,7Hz,1H), 8.23 (br s,1H). FAB-MS: calculated for $C_{19}H_{27}N_3O_4S$ 393; found 394 (M+H,36%).

Step B: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2′-(N-triphenylmethyl)-tetrazol-5-yl][1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4′-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, CD_3OD): 1.32 (s,6H), 1.39 (s,9H), 2.26 (d,7Hz,1H), 2.47 (d,14Hz,1H), 2.63 (d,14Hz,1H), 3.01 (t,11Hz,1H), 3.60 (dd;7,11Hz;1H), 4.76 (dd;7,11Hz;1H), 5.05 (br s,2H), 6.9-7.6 (m,26H), 7.80 (m,1H). FAB-MS (Li^+ spike): calculated for $C_{52}H_{51}N_7O_4S$ 870; found 876 (M+Li,100%).

Step C: 3-Amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, trifluoroacetate.

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 3l, Step H. ^{1}H NMR (200MHz, CD_3OD): 1.38 (s,3H), 1.40 (s,3H), 2.55 (br s,2H), 3.09 (t,11Hz,1H), 3.64 (dd;7,11Hz;1H), 4.65 (dd;7,11Hz;1H), 5.07 (d,15Hz,1H), 5.24 (d,15Hz,1H), 7.06 (d,8Hz,2H), 7.3-7.7 (m,10H). FAB-MS: calculated for $C_{28}H_{29}N_7O_2S$ 527; found 528 (M+H,100%).

Example 47

3-Amino-3-methyl-N-[3,4-dihydro-1,1,4-trioxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, trifluoroacetate

Step A: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-1,1,4-trioxo-1,5-benzothiazepin-3(S)-yl]-butanamide

To a solution of 88mg (0.22mmol) of 3-t-butoxycarbonylamino-3-methyl-N-[3,4-dihydro-4-oxo-1,5-benzothiazepin-3(S)-yl]-butanamide (Example 46, Step A) in 2mL of dry methylene chloride under nitrogen was added 38mg of solid sodium bicarbonate (0.44mmol, 2eq) followed by 106mg of 80% m-chloroperbenzoic acid (85mg mCPBA, 0.49mmol, 2.2eq). The mixture was stirred at room temperature for 3 hours then concentrated under vacuum. The residue was chromatographed on silica, eluting with ethyl acetate/hexane (7:3). The chromatographed material was redissolved in 50mL of ethyl acetate, washed with 1:1 saturated aqueous sodium chloride/saturated aqueous potassium carbonate, then brine, dried over magnesium sulfate, filtered and evaporated under vacuum to afford 86mg (0.20mmol, 91%) of the product. ^{1}H NMR (200MHz, $CDCl_3$): 1.36 (s,3H), 1.38 (s,3H), 1.45 (s,9H), 2.51 (d,13Hz,1H), 2.83 (d,13Hz,1H), 3.58 (dd;12,14Hz;1H), 4.33 (dd;8,14Hz;1H), 4.90 (m,2H), 7.30 (m,2H), 7.46 (t,8Hz,1H), 7.70 (t,8Hz,1H), 8.07 (d,8Hz,1H), 8.70 (br s,1H). FAB-MS: calculated for $C_{19}H_{27}N_3O_6S$ 425; found 426 (M+H,32%).

Step B: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-1,1,4-trioxo-5-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]-methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.35 (s,3H), 1.37 (s,3H), 1.47 (s,9H), 2.45 (d,13Hz,1H), 2.81 (d,13Hz,1H), 3.40 (dd;11,14Hz,1H), 4.18 (m,3H), 4.80 (m,2H), 5.65 (d,15Hz,1H), 6.9-7.6 (m,25H), 7.95 (m,2H). FAB-MS (Li^+ spike): calculated for $C_{52}H_{51}N_7O_6S$ 902; found 909 (M+Li,100%).

Step C: 3-Amino-3-methyl-N-[3,4-dihydro-1,1,4-trioxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, trifluoroacetate

Prepared from the intermediate obtained in Step B by the procedure described in Example 31, Step H. ^{1}H NMR (200MHz, CD_3OD): 1.32 (br s,6H). 2.51 (br s,2H), 3.64 (dd;12,14Hz,1H), 3.98 (dd;8.14;1H), 4.54 (d,16Hz,1H), 4.78 (m,1H), 5.43 (d,16Hz,1H), 7.08 (d,8Hz,2H), 7.30 (m,3H), 7.5-7.8 (m,6H), 8.00 (d,8Hz,1H). FAB-MS: calculated for $C_{28}H_{29}N_7O_4S$ 559; found 560 (M+H,100%).

Example 48

3-Amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, trifluoroacetate [diastereomer A]

Step A: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-1,4-dioxo-1,5-benzothiazepin-3(S)-yl]-butanamide, diastereomers A and B

A solution of 179mg (0.46mmol) of 3-t-butoxycarbonylamino-3-methyl-N-[3,4-dihydro-4-oxo-1,5-benzothiazepin-3(S)-yl]-butanamide (Example 46, Step A) in 4.5mL of methanol/water (5:1) was treated with 102mg (0.48mmol, 1.05eq) of sodium periodate and stirred at room temperature for 48 hours. The reaction mixture was filtered and the filtrate concentrated under vacuum. The residue was redissolved in chloroform, dried over potassium carbonate, filtered and concentrated under vacuum. Purification by flash chromatography on silica, eluting with ethyl acetate, afforded 47mg (0.12mmol, 25%) of the less polar, minor diastereomer A in addition to 105mg (0.26mmol, 56%) of the more polar, major diastereomer B.

^{1}H NMR (diastereomer A; 200MHz, $CDCl_3$): 1.37 (s,3H), 1.38 (s,3H), 1.45 (s,9H), 2.51 (d,13Hz,1H), 2.79 (d,13Hz,1H), 3.80 (m,2H), 4.78 (m,1H), 4.95 (br s,1H), 7.14 (m,2H), 7.59 (m,2H), 7.93 (m,1H), 8.18 (br s,1H). FAB-MS: calculated for $C_{19}H_{27}N_3O_5S$ 409; found 410 (M+H,29%).

Step B: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl)-butanamide, diastereomer A

Prepared from diastereomer A obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.35 (s,3H), 1.36 (s,3H), 1.44 (s,9H), 2.45 (d,13Hz,1H), 2.72 (d,13Hz,1H), 3.61 (m,2H), 4.63 (m,1H), 4.86 (m,2H), 6.9-7.6 (m,25H), 7.81 (m,1H), 7.90 (m,1H). FAB-MS (Li^+ spike): calculated for $C_{52}H_{51}N_7O_5S$ 886; found 893 (M+Li,95%).

Step C: 3-Amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, trifluoroacetate diastereomer A

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 31, Step H. ^{1}H NMR (200MHz, CD_3OD): 1.32 (br s,6H), 2.51 (br s,2H), 3.32 (dd;8,11Hz;1H), 3.95 (t,11Hz,1H), 4.55 (dd;8,11Hz;1H), 4.85 (d,15Hz,1H), 5.22 (d,15Hz,1H), 7.01 (d,8Hz,2H), 7.17 (d,8Hz,2H), 7.4-7.8 (m,8H). FAB-MS: calculated for $C_{28}H_{29}N_7O_3S$ 543; found 544 (M+H,100%).

Example 49

3-Amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, trifluoroacetate [diastereomer B]

Step A: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-1,4-dioxo-1,5-benzothiazepin-3(S)-yl]-butanamide, diastereomer B

Prepared from 3-t-butoxycarbonylamino-3-methyl-N-[3,4-dihydro-4-oxo-1,5-benzothiazepin-3(S)-yl]-butanamide (Example 46, Step A) by the procedure described in Example 48, Step A. ^{1}H NMR (diastereomer B; 200MHz, $CDCl_3$): 1.37 (s,3H), 1.38 (s,3H), 1.44 (s,9H), 2.48 (d,14Hz,1H), 2.68 (d,14Hz,1H), 3.30 (dd;11,15Hz;1H), 4.14 (dd;8,15Hz;1H), 4.86 (m,1H), 7.1 (d,8Hz,1H), 7.25 (m,1H), 7.41 (m,1H), 7.55 (m,1H), 8.81 (br s,1H). FAB-MS: calculated for $C_{19}H_{27}N_3O_5S$ 409; found 410 (M+H,38%).

Step B: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, diastereomer B

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.38 (s,6H), 1.45 (s,9H), 2.50 (d,14Hz,1H), 2.72 (d,14Hz,1H), 3.10 (dd;10,15Hz;1H), 4.05 (m,2H), 4.85 (m,1H), 5.08 (br s,1H), 5.68 (d,15Hz,1H), 6.9-7.5 (m,26H), 7.92 (m,1H). FAB-MS (Li^+ spike): calculated for $C_{52}H_{51}N_7O_5S$ 886; found 893 (M+Li,64%).

Step C: 3-Amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, trifluoroacetate, [diastereomer B]

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 31, Step H. ^{1}H NMR (200MHz, CD_3OD): 1.33 (br s,6H), 2.53 (br s,2H), 3.29 (dd;11,14Hz;1H), 3.89 (dd;7,14;1H), 4.48 (d,16Hz,1H), 4.82 (m,1H), 5.33 (d,16Hz,1H), 7.0-7.7 (m,12H). FAB-MS: calculated for $C_{28}H_{29}N_7O_3S$ 543; found 544 (M+H,100%).

Example 50

3-Amino-3-methyl-N-[3,4-dihydro-3-oxo-4-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1,4-benzothiazepin-2-yl]-butanamide, mono(trifluoroacetate)

Step A: 2-Amino-3,4-dihydro-3-oxo-2H-1,4-benzothiazine

Anhydrous ammonia gas was bubbled for one hour through a suspension of 500mg (2.5mmol) of 2-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (prepared by the method of Worley, et al; J. Org. Chem., 40, 1731-1734 (1975)) in 5mL of methylene chloride. The mixture was filtered through Celite and the filtrate evaporated under vacuum. The residue was triturated with 20mL of chloroform, filtered and the filtrate evaporated under vacuum. Purification by flash chromatography on silica, eluting with ethyl acetate, afforded 185mg (1.0mmol, 41%) of the product. ^{1}H NMR (200MHz, $CDCl_3$): 2.00 (br s,2H), 4.68 (br s,1H), 6.9-7.4 (m,4H), 9.05 (br s,1H). FAB-MS: calculated for $C_8H_8N_2OS$ 180; found 181 (M+H,54%).

Step B: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl]-butanamide

Prepared from 2-amino-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (Step A) and 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) by the procedure described in Example 1, Step F. ^{1}H NMR (200MHz, CD_3OD): 1.26 (s,6H), 1.36 (s,9H), 2.47 (d,13Hz,1H), 2.57 (d,13Hz,1H), 5.52 (br s,1H), 6.31 (br s,1H), 7.00 (m,2H), 7.22 (m,2H). FAB-MS: calculated for $C_{18}H_{25}N_3O_4S$ 379; found 380 (M+H,26%).

Step C: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-3-oxo-4-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-2H-1,4-benzothiazin-2-yl]-butanamide

Prepared from the intermediate obtained in Step B and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.40 (s,6H), 1.42

(s,9H), 2.53 (d,14Hz,1H), 2.92 (d,14Hz,1H), 4.86 (d,16Hz,1H), 4.92 (d,8Hz,1H), 5.29 (d,16Hz,1H), 5.49 (d,8Hz,1H), 6.85-7.50 (m,26H), 7.92 (m,1H).

Step D: 3-Amino-3-methyl-N-[3,4-dihydro-3-oxo-4-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1,4-benzothiazin-2-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 31, Step H. ^{1}H NMR (200MHz, CD_3OD): 1.40 (s,6H), 2.62 (s,2H), 5.34 (s,2H), 5.73 (s,1H), 7.0-7.7 (m,12H). FAB-MS: calculated for $C_{27}H_{27}N_7O_2S$ 513; found 514 (M+H,100%).

Example 51

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[2-phenylethyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

Step A 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-amino-2,3,4,5-tetrahydro-1H[1]benzazepin-2-one (Example 1, Step A) and 3-benzyloxycarbonylamino-3-methylbutanoic acid (Example 1, Step E) by the procedure described in Example 1, Step F. ^{1}H NMR (200MHz, $CDCl_3$): 1.38 (s,3H), 1.39 (s,3H), 1.82 (m,1H), 2.52 (s,2H), 2.5-3.0 (m,3H), 4.51 (m,1H), 5.07 (br s,2H), 5.58 (br s,1H), 6.68 (d,7Hz,1H), 6.96 (d,8Hz,1H), 7.1-7.4 (m,8H), 7.62 (br s,1H). FAB-MS: calculated for $C_{23}H_{27}N_3O_4$ 409; found 410 (M+H,100%).

Step B 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[2-phenylethyl]-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step A and 2-phenethyl bromide by the procedure described in Example 3, Step A. ^{1}H NMR (200MHz, $CDCl_3$): 1.37 (s,6H), 1.68 (m,2H), 2.50 (m,4H), 2.7-3.0 (m,2H), 3.70 (m,1H), 4.48 (m,2H), 5.05 (s,2H), 5.66 (s,1H), 6.99 (m,1H), 7.0-7.4 (m,14H). FAB-MS: calculated for $C_{31}H_{35}N_3O_4$ 513; found 514 (M+H,100%).

Step C 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[2-phenylethyl]-1H-1-benzazepin-3-yl]butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 3, Step B ^{1}H NMR (200MHz, CD_3OD): 1.34 (s,3H), 1.42 (s,3H), 2.0-2.4 (m,1H), 2.58 (m,3H), 2.85 (m,2H), 3.90 (m,1H), 4.58 (m,1H), 4.90 (d,15Hz,1H), 5.0 (m,1H), 5.15 (d,15Hz,1H), 7.0-7.5 (m,9H). FAB-MS: calculated for $C_{23}H_{29}N_3O_2$ 379; found 380 (M+1,100%).

Example 52

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[3-phenylpropyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

Step A 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[3-phenylpropyl]-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide (Example 51, Step A) and 3-phenylpropyl bromide by the procedure described in Example 3, Step A. ^{1}H NMR (200MHz, $CDCl_3$): 1.38 (s,6H), 1.82 (m,4H), 2.4-2.9 (m,7H), 3.45 (m,1H), 4.36 (m,1H), 5.02 (s,2H), 5.64 (s,1H), 6.69 (d,8Hz,1H), 6.9-7.4 (m,14H). FAB-MS: calculated for $C_{32}H_{37}N_3O_4$ 527; found 528 (M+H,100%).

Step B 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[3-phenylpropyl]-1H-1-benzazepin-3-yl]butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 3, Step B. ^{1}H NMR (200MHz. CD_3OD): 1.21 (s.6H). 1.7-2.1 (m.2H). 2.1-2.4 (m,2H), 2.5-2.9 (m.6H).

3.46 (m,1H). 4.37 (m.2H), 6.9-7.3 (m.9H). FAB-MS: calculated for $C_{24}H_{31}N_3O_2$ 393; found 394 (M+1,100°%).

Example 53

4-Amino-4-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-pentanamide, trifluoroacetate

Step A: 3-Amino-2,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one, hydrochioride

Prepared from 3-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1, Step A) by the procedures described in Example 4, Steps A, B and C. ^{1}H NMR (200MHz, CD_3OD): 2.17 (m,1H), 2.3-2.6 (m,3H), 3.80 (dd;8,12Hz;1H), 4.78 (d,15Hz,1H), 5.38 (d,15Hz,1H), 6.95 (d,8Hz,2H), 7.17 (d,8Hz,2H), 7.28 (m,2H), 7.38 (m,2H), 7.5-7.7 (m,4H). FAB-MS: calc. for $C_{24}H_{22}N_6O$ 410; found 411 (M+H,100%).

Step B: 4-Benzyloxycarbonylamino-4-methylpentanoic acid

Prepared from 2,2-dimethylglutaric acid by the procedures described in Example 1, Steps C, D and E. ^{1}H NMR (200MHz, $CDCl_3$): 1.29 (s,6H), 2.02 (t,6Hz,2H), 2.34 (t,6Hz,2H), 5.06 (s,2H), 7.34 (s,5H), 10.5 (br s,1H).

Step C: 4-Benzyloxycarbonylamino-4-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl-1H-benzazepin-3-yl]-pentanamide

Prepared from the intermediates obtained in Steps A and B by the procedure described in Example 4, Step D. ^{1}H NMR (200MHz, CD_3OD): 1.30 (s,6H), 1.9-2.6 (m,8H), 4.38 (m,1H), 4.86 (d,13Hz,1H), 4.98 (s,2H), 5.16 (d,13Hz,1H), 6.97 (d,8Hz,2H), 7.1-7.3 (m,11H), 7.4-7.7 (m,4H). FAB-MS: calculated for $C_{38}H_{39}N_7O_4$ 657; found 658 (M+H,20%).

Step D: 4-Amino-4-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-pentanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 1, Step H. ^{1}H NMR (200MHz, CD_3OD): 1.29 (s,3H), 1.31 (s,3H), 1.8-2.6 (m,8H), 4.29 (dd;8,12Hz;1H), 4.94 (d,13Hz,1H), 5.16 (d,13Hz,1H), 6.99 (d,8Hz,2H), 7.1-7.3 (m,6H), 7.4-7.7 (m,4H). FAB-MS: calculated for $C_{30}H_{33}N_7O_2$ 523; found 524 (M+H,100%)

Example 54

Piperidine-N'-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-4-carboxamide, trifluoroacetate

Step A: N-(t-Butoxycarbonyl)piperidine-4-carboxylic acid

To a suspension of 1.0g (7.74mmol) of piperidine-4-carboxylic acid in 20mL of methylene chloride at room temperature was added 1.13mL of triethylamine (0.82g, 8.1mmol, 1.05eq) followed by 1.87mL of di-t-butyl-dicarbonate (1.77g, 8.1mmol, 1.05eq). The mixture was stirred at room temperature for 48 hours then concentrated under vacuum. The residue was redissolved in ethyl acetate and the solution washed with 5% citric acid and brine, then dried over magnesium sulfate, filtered and evaporated under vacuum to afford 1.75g (7.63mmol, 98%) of the product. ^{1}H NMR (200MHz, CD_3OD): 1.42 (s,9H), 1.50 (m,2H), 1.84 (m,2H), 2.46 (m,1H), 2.86 (t,9Hz,2H), 3.91 (t,3Hz,1H), 3.98 (t,3Hz,1H). FAB-MS: calculated for $C_{11}H_{19}NO_4$ 229; found 230 (M+H,17%).

Step B: N-(t-butoxycarbonyl)piperidine-N'-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-piperidine-4-carboxamide

Prepared from N-(t-butoxycarbonyl)piperidine-4-carboxylic acid and 3-amino-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one hydrochloride (Example 53, Step A) by the procedure described in Example 4, Step D. ^{1}H NMR (200MHz, CD_3OD): 1.42 (s,9H), 1.4-2.9 (m,11H), 4.05 (m,3H), 4.30 (m,1H), 4.81 (d,15Hz,1H), 5.22 (d,15Hz,1H), 6.98 (d,8Hz,2H), 7.1-7.3 (m,6H), 7.4-7.7 (m,4H).

FAB-MS: calculated for $C_{35}H_{39}N_7O_4$ 621; found 622 (M+H,7%).

Step C: Piperidine-N'-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-4-carboxamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 31, Step H. ^{1}H NMR (200MHz, CD_3OD): 1.7-2.7 (m,8H), 3.00 (m,3H), 3.38 (m,2H), 4.31 (dd;8,12Hz;1H), 4.86 (d,15Hz,1H), 5.20 (d,15Hz,1H), 6.99 (d,8Hz,2H), 7.1-7.4 (m,6H), 7.4-7.7 (m,4H). FAB-MS: calculated for $C_{30}H_{31}N_7O_2$ 521; found 522 (M+H,100%).

Example 55

Piperidine-N'-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-3-carboxamide, trifluoroacetate

The title compound was prepared from piperidine-3-carboxylic acid and 3-amino-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one hydrochloride (Example 53, Step A) by the procedures described in Example 54. ^{1}H NMR (200MHz, CD_3OD): 1.6-2.2 (m,5H), 2.28 (m,1H), 2.50 (m,2H), 2.79 (m,1H), 3.19 (m,4H), 4.30 (m,1H), 4.86 (d,14Hz,1H), 5.17 (d,14Hz,1H), 6.99 (m,4H), 7.20 (m,4H), 7.55 (m,3H), 8.38 (m,1H). FAB-MS: calculated for $C_{30}H_{31}N_7O_2$ 521; found 522 (M+H,100%).

Example 56

Quinuclidine-N'-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepir-3-yl]-3-carboxamide, trifluoroacetate

The title compound, as a mixture of four diastereomers, was prepared from racemic quinuclidine-3-carboxylic acid and 3-amino-1,3,4,5-tetrahydro-1[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one hydrochloride (Example 53, Step A) by the procedures described in Example 4, Step D. ^{1}H NMR (200MHz, CD_3OD): 1.7-2.7 (m,8H), 3.0-3.7 (m,8H), 4.32 (m,1H), 4.8-5.2 (m,2H), 7.00 (d,8Hz,2H) 7.1-7.4 (m,6H), 7.4-7.7 (m,4H). FAB-MS: calculated for $C_{32}H_{33}N_7O_2$ 547; found 531 (22%).

Example 57

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 3-t-Butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1, Step B) by the procedure described in Example 1, Step F. ^{1}H NMR (200MHz, $CDCl_3$): 1.37 (s,6H), 1.44 (s,9H), 1.95 (m,1H), 2.46 (d,15Hz,1H), 2.59 (d,15Hz,1H), 2.6-3.0, (m,3H), 4.53 (m,1H), 5.30 (br s,1H), 6.72 (d,7Hz,1H), 6.98 (d,8Hz,1H), 7.1-7.3 (m,3H), 7.82 (br s,1H). FAB-MS: calculated for $C_{20}H_{29}N_3O_4$ 375; found 376 (M+H,70%).

Step B: 3-t-Butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[[1,1'-biphenyl)-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

Prepared from the intermediate obtained in Step A and 4-chloromethylbiphenyl by the procedure described in Example 1, Step K. FAB-MS: calculated for $C_{33}H_{39}N_3O_4$ 541; found 542 (M+H,31%).

Step C: 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 31, Step H. ^{1}H NMR (200MHz, CD_3OD): 1.33 (s,3H), 1.36 (s,3H), 2.0-2.6 (m,6H), 4.38 (dd;8,12Hz;1H), 4.89 (d,15Hz,1H), 5.24 (d,15Hz,1H), 7.1-7.6 (m,13H). FAB-MS: calculated for $C_{28}H_{31}N_3O_2$ 441; found 442

(M+H,100%).

Example 58

3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-carboxy][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide

Step A: 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and 3-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1, Step A) by the procedure described in Example 1, Step F. ^{1}H NMR (300MHz, $CDCl_3$): 1.34 (s,6H), 1.41 (s,9H), 1.90 (m,1H), 2.45 (d,15Hz,1H), 2.56 (d,15Hz,1H), 2.65 (m,1H), 2.76 (m,1H), 2.92 (m,1H), 4.53 (m,1H), 5.20 (br s,1H), 6.62 (d,7Hz,1H), 6.97 (d,8Hz,1H), 7.10-7.25 (m,3H), 7.35 (br s,1H). FAB-MS: calculated for $C_{20}H_{29}N_3O_4$ 375; found 376 (M+H,45%).

Step B: 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-t-butoxycarbonyl]-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step A and t-butyl 4'-bromomethylbiphenyl-2-carboxylate (prepared by the method of D. J. Carini, et al, EPO publication 324,377) by the procedure described in Example 1, Step K. ^{1}H NMR (300MHz, $CDCl_3$): 1.17 (s,9H), 1.34 (s,6H), 1.40 (s,9H), 1.86 (m,1H), 2.40-2.65 (m,5H), 4.51 (m,1H), 4.81 (d,14Hz,1H), 5.31 (s,1H), 5.35 (d,14Hz,1H), 6.68 (d,7Hz,1H), 7.1-7.5 (m,11H), 7.71 (m,1H). FAB-MS: calculated for $C_{38}H_{47}N_3O_6$ 641; found 642 (M+H,15%).

Step C: 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-carboxy][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide

The intermediate obtained in Step B (500mg, 0.78mmol) dissolved in 2mL of glacial acetic acid was treated with 2mL of 6N HCl and the mixture heated at 50°C for 3 hours. The mixture was concentrated under vacuum to a minimum volume, redissolved in 3mL of distilled water and lyophilized. The crusty solid was redissolved in 2mL of methanol and treated dropwise with stirring with 5mL of propylene oxide. The mixture was stirred at room temperature for 5 hours then filtered; the filter cake was washed with ether, air dried, then dried under vacuum to give 278mg (0.57mmol, 73%) of the title compound. ^{1}H NMR (300MHz, D_2O): 1.43 (s,3H), 1.47 (s,3H), 2.0-2.5 (m,4H), 2.66 (m,2H), 4.28 (dd;7,11Hz;1H), 4.70 (d,15Hz,1H), 5.29 (d,15Hz,1H), 6.92 (m,1H), 7.0-7.4 (m,10H), 7.70 (m,1H). FAB-MS: calculated for $C_{29}H_{31}N_3O_4$ 485; found 486 (M+H,100%).

Example 59

3-Amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

Step A: 7-Methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 6-methoxy-1-tetralone by the procedure described in Example 31, Step A. ^{1}H NMR (200MHz, $CDCl_3$): 2.1-2.4 (m,4H), 2.72 (t,7Hz,2H), 3.77 (s,3H), 6.71 (d,8Hz,2H), 6.73 (s,1H), 6.89 (d,8Hz,1H), 7.80 (br s, 1H). FAB-MS: calculated for $C_{11}H_{13}NO_2$ 191; found 191 (M^+,60%).

Step B: 3-Iodo-7-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 7-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step B. ^{1}H NMR (200MHz, $CDCl_3$): 2.5-3.0 (m,4H), 3.89 (s,3H), 4.64 (t,8Hz,1H), 6.75 (s,1H), 6.77 (d,8Hz,1H), 6.94 (d,8Hz,1H), 7.70 (br s, 1H). FAB-MS: calculated for $C_{11}H_{12}INO_2$ 317; found 317 (M^+,100%).

Step C: 3-Azido-7-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

3-Iodo-7-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (4.074g, 12.85mmol) and sodium azide (4.178g, 64.3mmol, 5eq.) were dissolved in 50mL of dimethylformamide and heated with stirring at 60° for 2 hours. The solvent was evaporated under vacuum at room temperature and the residue redissolved in 150mL

of ethyl acetate and washed with water (3x50mL) and brine (1x50mL). The organic layer was separated, dried over $MgSO_4$, filtered and evaporated to dryness under vacuum to yield 2.538g (10.94mmol, 85%) of product. ^1H NMR (200MHz, $CDCl_3$): 2.2-2.7 (m,3H), 2.90 (m,1H), 3.75 (s,3H), 3.80 (m,1H), 6.75 (m,2H), 6.95 (d,8Hz,2H), 8.22 (br s,1H). FAB-MS: calculated for $C_{11}H_{12}N_4O_2$ 232; found 233 (M+H,30%).

Step D: 3-Amino-7-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 3-azido-7-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step D. ^1H NMR (200MHz, $CDCl_3$): 1.86 (m,1H), 2.4-2.6 (m,2H), 2.86 (m,1H), 3.39 (m,1H), 3.76 (s,3H), 6.72 (d,8Hz,1H), 6.74 (s,1H), 6.88 (d,8Hz,1H), 7.62 (br s,1H). FAB-MS: calculated for $C_{11}H_{14}N_2O_2$ 206; found 208 (100%).

Step E: 3-t-Butoxycarbonylamino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and the amine obtained in Step D by the procedure described in Example 1, Step F. ^1H NMR (200MHz, $CDCl_3$): 1.32 (s,6H), 1.38 (s,9H), 1.86 (m,1H), 2.4-3.0 (m,5H), 3.77 (s,3H), 4.49 (m,1H), 5.25 (br s,1H), 6.68 (d,8Hz,1H), 6.70 (s,1H), 6.89 (d,8Hz,1H), 7.55 (br s,1H). FAB-MS: calculated for $C_{21}H_{31}N_3O_5$ 405; found 428 (M+Na,100%), 406 (M+H,23%).

Step F: 3-t-Butoxycarbonylamino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(N-triphenylmethyl)-tetrazol-5-yl][1,1′-biphenyl]-4-yl]methyl-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step E and N-triphenylmethyl-5-[2-(4′-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step G. ^1H NMR (200MHz, $CDCl_3$): 1.31 (s,3H), 1.32 (s,3H), 1.37 (s,9H), 1.70-(m,1H), 2.2-2.6 (m,5H), 3.72 (s,3H), 4.43 (m,1H), 4.61 (d,15Hz,1H), 5.06 (d,15Hz,1H), 5.35 (br s,1H), 6.62 (m,3H), 6.9 (m,10H), 7.25 (m,12H), 7.83 (m,1H).

Step G: 3-Amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl)-1H-1-benzazepin-3-yl]-butanamide, mono(trifluoroacetate)

The title compound was prepared from the intermediate obtained in Step F by the procedure described in Example 31, Step H. ^1H NMR (200MHz, CD_3OD): 1.35 (s,3H), 1.39 (s,3H), 2.05 (m,1H), 2.3-2.6 (m,5H), 3.81 (s,3H), 4.37 (dd;7,11Hz;1H), 4.76 (d,15Hz,1H), 5.22 (d,15Hz,1H), 6.80 (d,3Hz,1H), 6.88 (dd;3,8Hz;1H), 7.01 (d,8Hz,2H), 7.17 (d,8Hz,2H), 7.22 (d,8Hz,1H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{30}H_{33}N_7O_3$ 539; found 540 (M+H,100%).

Example 60

3-Amino-3-methyl-N-[7-hydroxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

240mg (0.27mmol) of 3-t-butoxycarbonylamino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(N-triphenylmethyl)-tetrazol-5-yl][1,1′-biphenyl]-4-yl]methyl-1H-1-benzazepin-3-yl]-butanamide (Example 59, Step F) was dissolved in 4mL of methylene chloride and the solution treated with 1.35mL of 1.0Mboron tribromide in methylene chloride (1.35mmol, 5eq.) and the mixture stirred at room temperature for 4 hours then quenched by the addition of 15mL of ice water. The mixture was extracted with ethyl acetate (2x20mL) and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and solvents removed in vacuo. The residue was purified by reverse phase medium pressure liquid chromatography on C8, eluting with methanol/0.1% aqueous trifluoroacetic acid (55:45). In this mauer, 56mg (0.087mmol, 32%) of the title compound was obtained as a colorless glass. ^1H NMR (200MHz, CD_3OD): 1.39 (s,3H), 1.43 (s,3H), 2.07 (m,1H), 2.3-2.6 (m,5H), 4.42 (dd;5,8Hz;1H), 4.79 (d,11Hz,1H), 5.24 (d,11Hz,1H), 6.68 (d,2Hz,1H), 6.78 (dd;2,7Hz;1H), 7.06 (d,7Hz,2H), 7.18 (d,7Hz,1H), 7.21 (d,7Hz,2H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{29}H_{31}N_7O_3$ 525; found 526 (M+H,87%).

Example 61

3-Amino-3-methyl-N-benzyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 3(R)-(Benzylamino)-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

A solution of 528mg (3.0mmol) of 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1, Step B) in 45mL of absolute methanol at room temperature was treated with 4.5g of powdered 3A molecular sieves followed by dropwise addition of a solution of 954mg (9.0mmol, 3eq.) of benzaldehyde in 15mL of methanol. The pH of the mixture was adjusted to 7 by addition of trifluoroacetic acid then stirred at room temperature for 2 hours. Sodium cyanoborohydride (18mL of 1.0M THF solution; 18mmol, 6eq.) was added and the mixture stirred at room temperature for 18 hours. The mixture was filtered and the filtrate treated with 3mL of trifluoroacetic acid with stirring for 3 hours, then all volatiles removed under vacuum and the residue dissolved in 50mL of ethyl acetate. The ethyl acetate solution was washed with water (3x15mL), saturated aqueous sodium bicarbonate (2x15mL) and 15mL of brine then dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue was purified by chromatography on silica, eluting with ethyl acetate/hexane (70:30), to afford 410mg (1.54mmol, 51%) of the product. ^{1}H NMR (200MHz,$CDCl_3$): 2.05 (m,1H), 2.5-3.0 (m,3H), 3.37 (dd;7,11Hz;1H), 3.57 (d,12Hz,1H), 3.90 (d,12Hz,1H), 7.05 (d,8Hz,1H), 7.1-7.4 (m,8H), 7.75 (br s,1H). FAB-MS: calculated for $C_{17}H_{18}N_2O$ 266; found 267 (M+H,75%).

Step B: 3-t-Butoxycarbonylamino-3-methyl-N-benzyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-(R)-yl]-butanamide

A solution of 90mg (0.34mmol) of 3(R)-(benzylamino)-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one in 1.5mL of tetrahydrofuran under nitrogen at room temperature was treated with 73mg (0.34mmol, 1eq.) of 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) followed by 94mg (0.38mmol, 1.1eq.) of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ). Most of the solvent was evaporated under a stream of nitrogen and the resulting reaction mixture (thick syrup approx. 0.3mL) was stirred for 3 days. The mixture was evaporated to dryness under vacuum and the residue purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate/hexane (1:1) to afford 45mg (mmol, 33%) of product. ^{1}H NMR (200MHz, $CDCl_3$): 1.28 (s,3H), 1.32 (s,3H), 1.35 (s,9H), 2.16 (m,2H), 2.35 (d,14Hz,1H), 2.58 (d,14Hz,1H), 2.60 (m,1H), 2.81 (m,1H), 4.70 (d,18Hz,1H), 4.99 (d,18Hz,1H), 5.37 (t,10Hz,1H), 5.83 (br s,1H), 6.98 (d,7Hz,1H), 7.05-7.45 (m,5H), 7.50-7.85 (m,3H), 8.13 (t,8Hz,1H), 8.90 (m,1H). FAB-MS: calculated for $C_{27}H_{35}N_3O_4$ 465; found 466 (M+H,48%).

Step C: 3-Amino-3-methyl-N-benzyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step B and N-triphenylmethyl-5-[2-(4′-bromomethylbiphen-4-yl)] tetrazole by the methods described in Example 1, Step K and Example 31, Step H. ^{1}H NMR (400MHz, CD_3CN): 1.35 (s,3H), 1.36 (s, 3H), 2.19 (m,1H), 2.38 (m,1H), 2.47 (d,17Hz,1H), 2.7-2.9 (m,2H), 2.90 (d,17Hz,1H), 4.75 (d,16Hz,1H), 4.93 (d,19Hz,1H), 5.03 (d,19Hz,1H), 5.22 (dd;8,12Hz;1H), 5.48 (d,16Hz,1H), 7.2-7.5 (m,10H), 7.6-7.8 (m,6H), 7.85 (br s,1H). FAB-MS: calculated for $C_{36}H_{37}N_7O_2$ 599; found 600 (M+H,30%).

Example 62

3-Amino-3-methyl-N-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 3(R)-N-Methyl-N-benzylamino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

A solution of 150mg (0.56mmol) of 3(R)-(benzylamino)-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 61, Step A) in 0.6mL of formic acid was treated with 0.047mL (0.56mmol, 1eq.) of 36% aqueous formaldehyde and the mixture heated at 80° with stirring for 24 hours. The mixture was cooled, treated with 0.8mL of 6N HCl and all volatiles removed under vacuum. The residue was partitioned between 10mL of water and 10mL of methylene chloride; 1mL of 10% aqueous sodium carbonate was then added and the mixture shaken. The organic layer was separated and the aqueous layer extracted with an additional 20mL of methylene chloride.

The combined extracts were dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with 2.5% methanol in ethyl acetate, to give 98mg (0.35mmol, 63%) of product. ^{1}H NMR (200MHz,$CDCl_3$): 2.35 (s,3H), 2.35 (m,2H), 2.69 (m,1H),2.88 (m,1H), 3.37 (dd;8,11Hz;1H),3.80 (d,14Hz,1H),3.90 (d,14Hz,1H),6.90 (d,8Hz,1H), 7.05-7.35 (m,8H). FAB-MS: calculated for $C_{18}H_{20}N_2O$ 280; found 281 (M+H,100%).

Step B: 3(R)-(methylamino)-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

A solution of 98mg (0.35mmol) of 3(R)-(N-methyl-N-benzyl)amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Step A) in 10mL of methanol was treated with one drop of concentrated sulfuric acid and the resulting solution hydrogenated at room temperature and 30-40psi over 20mg of 10% Pd/C for 20 hours. The mixture was filtered and the filtrate evaporated under vacuum. The residue was treated with 15mL of ethyl acetate, 4mL of water and 2mL of 10% aqueous sodium carbonate then shaken. The organic layer was separated, and the aqueous phase re-extracted with an additional 10mL of ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, filtered and the filtrate evaporated under vacuum to give 68mg (0.35mmol, 100%) of product. ^{1}H NMR (200MHz,$CDCl_3$): 1.85 (m,1H), 2.30 (s,3H), 2.35-2.65 (m,2H), 2.73 (m,1H), 3.10 (dd;8,12Hz;1H), 6.97 (d,8Hz,1H), 7.1-7.3 (m,3H), 7.5 (br s,1H).

Step C: 3-t-Butoxycarbonylamino-3-methyl-N-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-(R)-yl]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and the amine obtained in Step B by the procedure described in Example 1, Step F. ^{1}H NMR (200MHz, $CDCl_3$): 1.30 (br s,15H), 2.19 (m,1H), 2.42 (m,1H), 2.5-2.8 (m,3H), 2.91 (m,1H), 3.15 (s,3H), 5.32 (dd;6,8Hz;1H), 5.52 (br s,1H), 6.97 (d,5Hz,1H), 7.1-7.3 (m,3H), 7.35 (br s,1H).

Step D: 3-Amino-3-methyl-N-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Prepared from the intermediate obtained in Step C and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedures described in Example 1, Step K and Example 31 Step H. ^{1}H NMR (200MHz, CD_3OD):1.34(s,3H),1.38(s,3H),2.10 (m,1H),2.3-2.8 (m,5H),3.16 (s,3H),4.90 (d,15Hz,1H),5.01 (dd;7,11Hz; 1H),5.13 (d,15Hz,1H),7.02 (d,8Hz,2H), 7.19 (d,8Hz,2H),7.2-7.4 (m,4H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{30}H_{33}N_7O_2$ 523; found 524 (M+H,22%).

Example 63

2-Amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl-]propanamide, trifluoroacetate

Step A: 2-(t-Butoxycarbonylamino)-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-propanamide

Prepared from 2-(t-butoxycarbonylamino)-2-methylpropanoic acid and 3(R)-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Example 1, Step B) by the procedure described in Example 1, Step F. ^{1}H NMR (200MHz, $CDCl_3$): 1.42 (s,12H), 1.46 (s,3H), 1.90 (m,1H), 2.5-3.0 (m,3H), 4.48 (m,1H), 5.01 (br s,1H), 6.97 (d,8Hz,1H), 7.1-7.3 (m,3H), 7.9 (br s,1H). FAB-MS: calculated for $C_{19}H_{27}N_3O_4$ 361; found 362 (M+H,30%),

Step B: 2-(t-Butoxycarbonylamino)-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.42 (s,9H), 1.43 (s,3H), 1.46 (s,3H), 1.77 (m,1H), 2.2-2.7 (m,3H), 4.43 (m,1H), 4.72 (d,15Hz,1H), 4.93 (br s,1H), 5.09 (d,15Hz,1H), 6.9-7.5 (m,26H), 7.86 (m,1H).

Step C: 2-Amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoroacetate)

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 31, Step H with final purification performed by reverse phase medium pressure liquid chromatography on C-8, eluting with methanol/0.1% aqueous trifluoroacetic acid (55:45). ^{1}H-NMR (200MHz, CD_3OD): 1.52 (s,3H), 1.61 (s,3H), 2.1-2.6 (m,4H), 4.33 (dd;8,11Hz;1H), 4.85 (d,15Hz,1H), 5.18 (d,15Hz,1H), 6.99 (d,8Hz,2H), 7.15 (d,8Hz,2H), 7.2-7.4 (m,4H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{28}H_{29}N_7O_2$ 495; found 496 (M+H,32%).

Example 64

Quinuclidine-N'-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-3-carboxamide, trifluoroacetate

The title compound, as a mixture of two diastereomers, was prepared from racemic quinuclidine-3-carboxylic acid and 3(R)-amino-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one hydrochloride (Example 4, Step C) by the procedure described in Example 4, Step D, with final purification by reverse phase medium pressure liquid chromatography on C-8, eluting with acetonitrile/0.1 % aqueous trifluoroacetic acid (35:65). ^{1}H NMR (200MHz, CD_3OD): 1.7-2.6 (m,8H), 3.00 (m,1H), 3.1-3.3 (m,6H), 3.65 (m,1H), 4.32 (m,1H), 4.8-5.2 (m,2H), 7.00 (d,8Hz,2H), 7.1-7.3 (m,6H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{32}H_{33}N_7O_2$ 547; found 548 (M+H,100%).

Example 65

3-amino-2,2-dimethyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, trifluoroacetate

Step A: 3-(Benzyloxycarbonylamino)-2,2-dimethylpropanoic acid

Prepared from 3-[benzyloxycarbonylamino]-2,2-dimethylpropanoic acid, methyl ester (Example 1, Step D) by the procedure described in Example 1,Step E. ^{1}H NMR (200MHz, $CDCl_3$): 1.25 (s,6H), 3.30 (d,7Hz,2H), 5.10 (s,2H), 7.34 (s,5H).

Step B: 3-(Benzyloxycarbonylamino)-2,2-dimethyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-propanamide

Prepared from 3-(benzyloxycarbonylamino)-2,2-dimethylpropanoic acid and 3(R)-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Example 1, Step B) by the procedure described in Example 1, Step F. ^{1}H NMR (200MHz, $CDCl_3$): 1.19 (s,6H), 1.90 (m,1H), 2.6-3.0 (m,3H), 3.26 (d,6Hz,2H), 4.46 (m,1H), 5.07 (s,2H), 5.7 (br t,1H), 6.62 (d,7Hz,1H), 6.97 (d,8Hz,1H), 7.1-7.3 (m,3H), 7.3 (s,5H), 8.14 (br s,1H). FAB-MS: calculated for $C_{23}H_{27}N_3O_4$ 409; found 410 (M+H,100%),

Step C: 3-(t-Butoxycarbonylamino)-2,2-dimethyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-propanamide

A solution of 170mg (0.42mmol) of the intermediate obtained in Step B in 5mL of absolute methanol and one drop of trifluoroacetic acid was hydrogenated at room temperature and 1 atmosphere over 35mg of 20% palladium hydroxide on carbon for 4 hours. The mixture was filtered through Celite and solvent removed under vacuum to afford 165mg (0.42mmol, 100%) of the amine trifluoroacetate salt as a pale yellow solid.

The above intermediate was dissolved in 2mL of methylene chloride and treated with 108mg (0.49mmol, 1.2eq.) of di-t-butyl-dicarbonate followed by 0.12mL of triethylamine (87mg, 0.86mmol, 2eq.). After two hours at room temperature, the mixture was added to 20mL of ethyl acetate and washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate and brine. The organic layer was separated, dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate/hexane (3:2) to afford 156mg (0.41mmol, 98%) of the product as a white solid. ^{1}H NMR (200MHz, $CDCl_3$): 1.18 (s,6H), 1.39 (s,9H), 1.92 (m,1H), 2.6-3.0 (m,3H), 3.17 (d,6Hz,2H), 4.46 (m,1H), 5.25 (br s,1H), 6.69 (d,7Hz,1H), 6.98 (d,8Hz,1H), 7.1-7.3 (m,3H), 8.22 (br s,1H). FAB-

MS: calc. for $C_{20}H_{29}N_3O_4$ 375; found 376 (M+H,10%).

Step D: 3-(t-Butoxycarbonylamino)-2,2-dimethyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide

Prepared from the intermediate obtained in Step C and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.16 (s,3H), 1.17 (s,3H), 1.40 (s,9H), 1.74 (m,1H), 2.3-2.5 (m,3H), 3.16 (d,7Hz,2H), 4.40 (m,1H), 4.62 (d,15Hz,1H), 5.22 (d,15Hz,1H), 5.28 (br s,1H), 6.68 (d,7Hz,1H), 6.9-7.5 (m,26H), 7.85 (m,1H).

Step E: 3-Amino-2,2-dimethyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step D by the procedure described in Example 31, Step H with final purification performed by reverse phase medium pressure liquid chromatography on C-8, eluting with methanol/0.1% aqueous trifluoroacetic acid (55:45). ^{1}H NMR (200MHz, CD_3OD): 1.24 (s,3H), 1.33 (s,3H), 2.1-2.6 (m,4H), 2.99 (br s,2H), 4.30 (dd;8,11Hz;1H), 4.85 (d,15Hz,1H), 5.21 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.1-7.4 (m,6H), 7.4-7.7 (m,4H). FAB-MS: calculated for $C_{29}H_{31}N_7O_2$ 509; found 510 (M+H,100%).

Example 66

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(S)-yl]-butanamide, trifluoroacetate

Step A: 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(S)-yl]-butanamide

Prepared from 3(S)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1, Step B) and 3-benzyloxycarbonylamino-3-methylbutanoic acid (Example 1, Step E) by the procedure described in Example 1, Step F. FAB-MS: calculated for $C_{23}H_{27}N_3O_4$ 409; found 410 (M+H,100%). $[a]_D$= ⁻160° (c=1,$CHCl_3$).

Step B: 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(S)-yl]-butanamide

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-(4'-bromomethylbiphen-2-yl)tetrazole by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz,$CDCl_3$): 1.38 (s,3H), 1.40 (s,3H), 1.67 (m,1H), 2.2-2.5 (m,5H), 4.44 (m,1H), 4.67 (d,14Hz,1H), 5.06 (s,2H), 5.12 (d,14Hz,1H), 5.63 (br s,1H), 6.64 (d,7Hz,1H), 6.9-7.5 (m,31H), 7.85 (m,1H).

Step C: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(S)-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 1, Step L. ^{1}H NMR (200MHz,CD_3OD): 1.34 (s,3H), 1.38 (s,3H), 2.0-2.6 (m,6H), 4.34 (dd;7,11Hz;1H), 4.86 (d,15Hz,1H), 5.20 (d,15Hz,1H), 6.99 (d,8Hz,2H), 7.1-7.3 (m,6H), 7.45-7.70 (m,4H). FAB-MS: calculated for $C_{29}H_{31}N_7O_2$ 509; found 510 (M+H,100%). $[a]_D$= ⁻98° (c=.5,CH_3OH).

Example 67

3-(2-Fluoropropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

To a cold (-78°C) solution of 3-(2-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]butanamide (Example 22, 20mg, 0.029mmol) in 1.5mL of hydrogen fluoride-pyridine under a nitrogen atmosphere, 0.2mL of DAST (diethylaminosulfur trifluoride) was slowly added. The reaction mixture was brought to room temperature and stirred for 48 hours. Additional DAST (0.2mL) was added at 24 hour intervals until no further reaction was detected by

HPLC. The reaction mixture was repeatedly purified by reverse phase HPLC to afford 4mg of product. FAB-MS: calculated for $C_{32}H_{36}N_7O_2F$ 569; found 570 (M+H, 100%). The product was converted into its hydrochloride salt by repeated evaporation of an aqueous 6N HCl/methanol solution. ^{19}F NMR (CD_3OD): -75.4.

Example 68

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

Step A: 3-Nitro-4-phenyltoluene

To a cold (0°C) solution of 4-methyl-2-nitroaniline (3.8g) in 11mL of HBF_4, an aqueous solution of sodium nitrite (1.7g in 3.4mL) was added dropwise. The reaction mixture was stirred for 10 minutes. The precipitate was collected and washed with cold aqueous HBF_4 (3mL), ethanol and ether to yield 1.72g of diazonium salt. The diazonium salt was suspended in benzene (76mL) and acetonitrile (7.6mL). Potassium acetate (1.53g) was added and the resulting mixture stirred under nitrogen in the dark at room temperature for 1.5 hr. The solid was removed by filtration and the filtrate washed with water (2x) and brine. The solution was dried with anhydrous sodium sulfate and then concentrated to afford 1.49g of crude product which could be chromatographed on silica gel (2:1 hexanes:CH_2Cl_2).

Step B: 3-Amino-4-phenyltoluene

A solution of 2.4g of 3-nitro-4-phenyltoluene in 25mL of methanol was hydrogenated at room temperature and 40psi over 0.30g of 5% Pd/C catalyst. The solution was filtered and the filtrate concentrated to give 1.98g of product. EI-MS: calculated for $C_{13}H_{13}N$: 183; found 183.

Step C: 3-Cyano-4-phenyltoluene

To a cold (0°C) suspension of 3-amino-4-phenyltoluene (1.97g) in 2.65mL of water and 2.65mL of 12N HCl was slowly added a solution of sodium nitrite (738mg) in 2mL of water. To this yellowish slurry, 10mL of fluoroboric acid was added with stirring. The cold mixture was filtered and the solid (2.02g) washed with cold fluoroboric acid, ethanol and ether. A solution of this diazonium salt (2.02g) in 5mL of DMSO was added dropwise with cooling to a mixture of CuCN and NaCN in DMSO (13.3mL). The reaction mixture was then diluted with water (20mL) and extracted repeatedly with benzene. The combined organic layers were washed with water (2x) and brine and then dried over anhydrous $MgSO_4$. Concentration under vacuum gave a reddish oil which was chromatographed on silica gel to give 0.788g of product.

Step D: N-Triphenylmethyl-5-[2'-(4'-methylbiphenyl-4-yl)]tetrazole

A solution of 3-cyano-4-phenyltoluene (390mg) and trimethyltin azide (525mg) in 2.5mL of toluene was heated at reflux for 24hr under nitrogen. The reaction mixture was concentrated and the residue suspended in 3.5mL of toluene. Tetrahydrofuran (0.25mL) was added followed by HCl gas until the solution became homogenous. The mixture was concentrated and the residue (307mg) dissolved in 5mL of CH_2Cl_2 and treated with 504mg of triphenylmethyl chloride and 233mg of triethylamine under nitrogen. The mixture was stirred overnight and then diluted with CH_2Cl_2 and water. The layers were separated and the aqueous layer further extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, then dried over anhydrous magnesium sulfate. Concentration under vacuum afforded 935mg which was chromatographed on silica gel eluting with hexanes:ethyl acetate (9:1) to give 615mg of product.

Step E: N-Triphenylmethyl-5-[2'-(4'-bromomethylbiphenyl-4-yl)]tetrazole

A solution of N-triphenylmethyl-5-[2'-(methylbiphenyl-4-yl)]tetrazole (95.7mg), N-bromosuccinimide (35.5mg) and AIBN (2mg) in 4mL of CCl_4 was heated at reflux for 4hr. The reaction mixture was filtered and the filtrate concentrated to give 129mg of product.

Step F: 3-t-Butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-benzazepin-3(R)-yl]butanamide

To a solution of 33.7mg of 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzaepin-3(R)-yl]butanamide (Example 57, Step A) in 0.5mL of dry dimethylformamide at room temperature was added 3.6mg of 60% sodium hydride oil dispersion under nitrogen. After 30 minutes, N-triphenylmethyl-5-[2'-(4'-bromomethylbiphenyl-4-yl)]-tetrazole (129mg) in 0.2mL of dry dimethylformamide was added and the resulting mixture stirred for 8hr at room temperature. The mixture was diluted with ethyl acetate and washed with water (2x) and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated unde vacuum. The crude product was chromatographed on silica gel eluting with ethyl acetate:hexanes (2:1) to give 16mg of pure product. FAB-MS: calculated for $C_{53}H_{53}N_7O_2$ 851; found 858 (M+Li).

Step G: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]butanamide

A solution of 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-benzaepin-3(R)-yl]butanamide (14mg) in 0.3mL of methanol and 0.3mL of 9N HCl was stirred overnight at room temperature and under nitrogen. The reaction mixture was diluted with benzene and freeze-dried to give 12mg of crude product which was purified by RP-HPLC on a Dynamax C18 column, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol to 20% methanol in ten minutes) to give 9.0mg of the title compound. FAB-MS: calculated for $C_{29}H_{31}N_7O_2$ 510; found 511 (M+1). ^{1}H NMR (400MHz,CD_3OD): 1.35 (s,3H), 1.38 (s,3H), 2.1-2.85 (m,6H), 4.39 (dd;8,13Hz;1H), 4.95 (d,16Hz,1H), 5.39 (d,16Hz,1H), 7.1 (m,2H), 7.2-7.32 (m,7H), 7.55-7.70 (m,3H).

Example 69

4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide, trifluoroacetate

Step A: 4-Methylphenyltrimethylstannane

41.4L of 1.0 M p-tolylmagnesium bromide in diethyl ether (41.4mol) was added dropwise, maintaining the temperature below -5°C, over 4 hours to a solution of 546g (2.79mol) of trimethyltin chloride in tetrahydrofuran (4L) under nitrogen at -10°C. The suspension was allowed to warm slowly to room temperature over 12h then saturated ammonium chloride solution (1L) was added followed by sufficient water (approximately 1L) to dissolve the precipitate. The solution was extracted with ether-hexane (1:1) (1x4L, 3x2L). The combined organic phases were washed with brine, dried over magnesium sulfate and the solvents removed under vacuum. Purification by flash chromatography on silica gel eluting with hexane/ethyl acetate (95:5) gave a pale yellow oil containing white crystals of 4,4'-dimethylbiphenyl which were removed by filtration to leave 711.3g (100%) of product. ^{1}H NMR (300MHz,$CDCl_3$): 0.30 (s,9H), 2.34 (s,3H), 7.19 (d,7.7Hz,2H), 7.40 (d,7.7Hz,2H).

Step B: 4'-Methyl-1,1'-biphenyl-2-nitrile

A solution of 2.0g (10.98mmol) of 2-bromobenzonitrile, 2.93g (11.54mmol) of 4-methylphenyl-trimethylstannane (Step A) and 0.385g (0.55mmol) of bis-triphenylphosphine palladium (II) chloride in 50mL of dry dimethylformamide under nitrogen was heated at 100°C for 5.5 hours. The reaction was cooled to room temperature. The reaction was poured into 150mL of water and extracted with ether (3x150mL). The combined ether extracts were washed with water (4x100mL) and brine (100mL), dried over magnesium sulfate, filtered and the solvents removed under vacuum. Purification by flash chromatography on silica gel, eluting with hexane/ether (85:15), afforded 1.69g (80%) of the product contaminated with about 10% of 2-methylbenzonitrile. ^{1}H NMR (200MHz,$CDCl_3$): 2.40 (s,3H), 7.27 (d,7Hz,2H), 7.30-7.65 (m,5H), 7.72 (d,6Hz,1H). FAB-MS: calculated for $C_{14}H_{11}N$ 193; found 193 (M+,100%).

Step C: 4'-Bromomethyl-1,1'-biphenyl-2-nitrile

To a solution of 699mg (3.62mmol) of the intermediate obtained in Step B in 15mL of carbon tetrachloride under nitrogen was added 708.3mg (3.98mmol. 1.1 eq) of N-bromosuccinimide and 59mg (0.36mmol, 0.1eq) of azobisisobutyronitrile (AIBN). The resulting mirture was heated in the dark for 4 hours. The mixture was

cooled to room temperature and filtered. The filtrate was concentrated under vacuum to afford 948mg (96%) of the product as a yellow solid. ^{1}H NMR (200MHz,$CDCl_3$): 4.51 (s,2H), 7.25-7.80 (m,8H). FAB-MS: calculated for C14H10BrN 272; found 272,274 (M+).^{1}H NMR indicates the presence of minor amounts of starting material and dibromo derivative.

Step D: 3-[[1-[[2'-Cyano-[1,1'-biphenyl]-4-yl]-methyl]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepin-3(R)-yl)amino]-1,1-dimethyl-3-oxopropylcarbamic acid, 1,1-dimethylethyl ester

To a solution of 0.83g (2.21mmol) of 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) in 6mL of dry dimethylformamide at room temperature under nitrogen was added 97mg of 60% sodium hydride dispersion in oil (58mg NaH, 2.43mmol, 1.1 eq). After stirring for 1 hour, a solution of 780mg (2.88mmol, 1.3 eq) of 4'-bromomethyl-1,1'-biphenyl-2-nitrile (Step C) in 2.0mL of dimethylformamide was added via cannula. The flask which originally contained the bromide was washed with 1mL of dry dimethylformamide which was then added to the reaction mixture via cannula. After stirring at room temperature for 3 hours, the reaction was diluted with 200mL of ethyl acetate, washed with 50mL of water and 50mL of brine. The organic layer was separated, dried over magnesium sulfate, filtered and the solvent removed under vacuum. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexane (6:4), to afford 1.13g (90%) of the product as a white foam. ^{1}H NMR (200MHz,$CDCl_3$): 1.32 (s,3H), 1.40 (s,12H), 1.85 (m,1H), 2.35-2.70 (m,5H), 4.52 (m,1H), 4.90 (d,12Hz,1H), 5.21 (d,12Hz,1H), 6.70 (d,5Hz,1H), 7.10-7.65 (m,12H), 7.72 (d,6Hz,1H). FAB-MS: calculated for $C_{34}H_{38}N_4O_4$ 566; found 567 (M+H).

Step E: 4'-[[3(R)-[(3-t-Butoxycarbonylamino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide

To a solution of 600mg (1.06mmol) of intermediate from Step D in 3.0mL of dimethylsulfoxide was added 15mg (0.106mmol) of anhydrous potassium carbonate followed by 0.88mL of 30% aqueous hydrogen peroxide. The resulting mixture was stirred at room temperature for 24 hours. The reaction was diluted with 100mL of chloroform and washed with water (30mL), 50% saturated aqueous sodium bisulfite (30mL) and brine (30mL). The organic layer was dried over sodium sulfate, filtered and the solvent removed under vacuum. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford 551.4mg (90%) of the product as a white solid. ^{1}H NMR (200MHz,$CDCl_3$): 1.30 (s,3H), 1.37 (s,12H), 1.85 (m,1H), 2.45-2.70 (m,5H), 4.50 (m,1H), 4.85 (d,12Hz,1H), 5.18 (s,1H), 5.25 (d,12Hz,1H), 5.65 (s,1H), 6.78 (d,5Hz,1H), 7.2-7.5 (m,12H), 7.70 (dd;5,1Hz;1H). FAB-MS: calculated for $C_{34}H_{40}N_4O_5$ 584; found 586.

Step F: 4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

To a slurry of 551mg (0.942mmol) of intermediate from Step E in 2mL of dry methylene chloride was added 5 drops of anisole followed by 2mL of trifluoroacetic acid. After stirring for 2 hours at room temperature all volatiles were removed under vacuum. The resulting material was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/0.1% aqueous trifluoroacetic acid (55:45) to afford 535mg (95%) of the title compound as a white solid. ^{1}H NMR (200MHz,CD_3OD): 1.42 (s,3H), 1.48 (s,3H), 2.00-2.65 (m,6H), 4.42 (dd;7,10Hz;1H), 4.95 (d,14Hz,1H), 5.25 (d,14Hz,1H), 7.2-7.6 (m,12H). FAB-MS: calculated for $C_{29}H_{32}N_4O_3$ 484; found 485 (M+H,100%).

Example 70

4'-[[2,3,4,5-Tetrahydro-3(R)-[[3-[(2(R)-hydroxypropyl)amino]-3-methyl-1-oxobutyl]amino-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

To a solution of 0.75g (1.25mmol) of 4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide, trifluoroacetate (Example 69) in 15mL dry methanol was added 0.35mL (2.50mmol) of triethylamine, 4.0g of dry 4A powdered molecular sieves followed by a solution of 1.3g (7.5mmol) of 2(R)-benzyloxypropanal (prepared according to the procedure of Hanessian and Kloss, Tetrahedron Lett. 1985, 26, 1261-1264.) in 5mL of dry methanol. The pH of the mixture was carefully adjusted to 6.5 with glacial acetic acid. The reaction was stirred for 5 hours at which time 7.5mL (7.5mmol) of a 1.0 M solution of sodium cyanoborohydride in tetrahydrofuran was added by syringe. The reaction was stirred

for 3 days then filtered through a pad of Celite. To the filtrate was added 5.0mL of trifluoroacetic acid (CAUTION! evolution of hydrogen cyanide) and the resulting mixture stirred for three hours. The solvent was removed under vacuum to afford 5.0g of a clear oil.

The crude intermediate was dissolved in 30mL of methanol and placed in a shaker bottle. To the solution was added 1mL of trifluoroacetic acid followed by 1.2g of 30% palladium on carbon. The mixture was hydrogenated at room temperature and 40psi for 36 hours. The mixture was filtered through Celite and the solvent removed under vacuum. The resulting material was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/0.1% aqueous trifluoroacetic acid (60:40) to afford 640mg (78%) of the title compound as a white solid. ^{1}H NMR (200MHz,CD_3OD): 1.22 (d,8Hz,3H), 1.35 (s,3H), 1.39 (s,3H), 2.12 (m,2H), 2.32 (m,2H), 2.62 (m,4H), 2.80 (dd;8,11Hz;1H), 3.08 (dd;3,11Hz;1H), 3.92 (m,1H), 4.39 (dd;7,12Hz;1H), 5.02 (d,14Hz,1H), 5.18 (d,14Hz,1H), 7.20-7.55 (m,12H). FAB-MS: calculated for $C_{32}H_{36}N_4O_4$ 542; found 544 (M+H,100%).

Example 71

4'-[[3(R)-[[3-[(2(S),3-Dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl)methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

To a solution of 0.585g (0.98mmol) of 4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide, trifluoroacetate (Example 69) in 15mL dry methanol was added 0.27mL (1.95mmol) of triethylamine, 2.5g of dry 4A powdered molecular sieves followed by a solution of 1.3g (10mmol) of D-glyceraldehyde acetonide (used crude as prepared according to the procedure of Hertel, L.W.; Grossman, C. S.; Kroin, J.S. Synth. Comm. 1991, 21, 151-154.) in 5mL of dry methanol. The pH of the mixture was carefully adjusted to 6.5 with glacial acetic acid (7 drops). The reaction was stirred for 3 hours at which time 4.9mL (4.9mmol) of a 1.0M solution of sodium cyanoborohydride in tetrahydrofuran was added via syringe. The reaction was stirred for 20 hours then filtered through a pad of Celite. To the filtrate was added 5.0mL of trifluoroacetic acid (CAUTION! hydrogen cyanide evolved), 5.0ml of water and 5 drops of concentrated hydrochloric acid. The resulting mixture was stirred for 24 hours. The solvent was removed under vacuum to afford a clear oil which was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/ 0.1% aqueous trifluoroacetic acid (60:40) to afford 590mg (90%) of the title compound as a white solid. ^{1}H NMR (200MHz,CD_3OD): 1.35 (s,3H), 1.39 (s,3H), 2.12 (m,1H), 2.31 (m,1H), 2.60 (m,4H), 2.98 (dd;8,12Hz;1H), 3.19 (dd;3,12Hz;1H), 3.55 (dd;3,6Hz;2H), 3.83 (m,1H), 4.40 (dd;8,11Hz;1H), 5.02 (d,15Hz,1H), 5.15 (d,15Hz,1H), 7.20-7.55 (m,12H). FAB-MS: calculated for $C_{32}H_{38}N_4O_5$ 558; found 560 (100%).

Example 72

N-Ethyl-4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

Step A: 4'-[[2,3,4,5-Tetrahydro-3(R)-[[3-methyl-1-oxo-3-[[(benzyloxy)carbonyl]amino]butyl]-amino]-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxylic acid 1.1-dimethylethyl ester

To a solution of 1.22g (3.0mmol) of 3-benzyl-oxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example-1, Step F) in 10mL of dry dimethylformamide under nitrogen was added 131.6mg (3.29mmol) of 60% sodium hydride in oil. After stirring for 20 minutes, a solution of 1.14g (3.29mmol) of t-butyl 4'-bromomethyl-1,1'-biphenyl-2-carboxylate (prepared according to the procedure of D.J. Carini, et. al. EPO publication 324,377) in 2.5mL of dimethylformamide was added by cannula. The flask which originally contained the bromide was rinsed with 2.5mL dimethylformamide which was added to the reaction mixture. After stirring at room temperature for 2 hours, the reaction was diluted with 400mL of ethyl acetate, washed with 100mL of water and 100mL of brine. The organic layer was dried over magnesium sulfate, filtered and the solvent removed under vacuum. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/hexane (55:45) to afford 1.74g (96%) of the product as a white foam. ^{1}H NMR (200MHz-,$CDCl_3$): 1.15 (s,9H), 1.45 (s,3H), 1.48 (s,3H), 1.76 (m,1H), 2.35-2.62 (m,5H), 4.48 (m,1H), 4.79 (d,14Hz,1H), 5.04 (t,12Hz,2H), 5.35 (d, 14Hz,1H), 6.70 (d,6Hz,1H), 7.10-7.45 (m,17H), 7.72 (m,1H). FAB-MS: calculated for $C_{41}H_{45}N_3O_6$ 675; found 683 (M+Li).

Step B: 4'-[[2,3,4,5-Tetrahydro-3(R)-[[3-methyl-1-oxo-3-[[(benzyloxy)carbonyl]amino]butyl]-amino]-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxylic acid

To a solution of 150mg (0.22mmol) of fhe intermediate from Step A in 1mL of dry methylene chloride was added 2 drops of anisole followed by 1mL of trifluoroacetic acid. The solution was stirred for 4 hours at room temperature. The solvent was removed under vacuum and the resulting oil was azeotroped with carbon tetrachloride (3x20mL) to afford 140mg (100%) of product as a white foam. ^{1}H RMN (200MHz,$CDCl_3$): 1.38 (s,6H), 1.65 (m,1H), 2.10-2.40 (m,3H), 2.61 (s,2H), 4.45 (m,1H), 4.62 (d,14Hz,1H), 5.06 (s,2H), 5.27 (d,14Hz,1H), 7.00-7.36 (m,15H), 7.42 (m,1H), 7.55 (m,1H), 7.68 (d,7Hz,1H), 7.95 (dd;2,8Hz;1H), 8.18 (br s,1H). FAB-MS: calculated for $C_{37}H_{37}N_3O_6$ 619; found 642 (M+Na).

Step C: N-Ethyl-4'-[[3(R)-[[3-(benzyloxycarbonyl)-amino-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl][1,1'biphenyl]-2-carboxamide

To a slurry of 14mg (0.169mmol) of ethylamine hydrochloride in 1mL of dry methylene chloride under nitrogen at 0°C was added 0.047mL (0.339mmol) of triethylamine followed by a solution of 70mg (0.113mmol) of the intermediate from Step B in 1mL of methylene chloride. To this mixture was added 75mg (0.169mmol) of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate. The reaction mirture was slowly warmed to room temperature. After 2 hours the reaction was diluted with 75mL of ethyl acetate, washed with 25mL of 5% aqueous citric acid, 25mL of saturated aqueous sodium bicarbonate and 25mL of brine. The organic layer was dried over magnesium sulfate, filtered and the solvent removed urder vacuum. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/hexane (9:1) to afford 74mg (100%) of the product as a white foam. ^{1}H NMR (200MHz,$CDCl_3$): 0.75 (t,6Hz,3H), 1.35 (s,3H), 1.38 (s,3H), 1.76 (m,2H), 2.35-2.62 (m,5H), 3.10 (m,2H), 4.48 (m,1H), 4.82 (d,14Hz,1H), 5.04 (m,3H), 5.30 (d,14Hz,1H), 5.57 (s,1H), 6.65 (d,6Hz,1H), 7.10-7.45 (m,15H), 7.62 (m,1H). FAB-MS: calculated for $C_{39}H_{42}N_4O_5$ 646; found 669 (M+Na).

Step D: N-Ethyl-4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

To a solution of 74mg (0.114mmol) of the intermediate obtained in Step C in 5mL of dry methanol was added 3 drops of trifluoroacetic acid and 15mg of 20% palladium hydroxide on carbon. The mixture was hydrogenated at room temperature and 40psi for 3 hours. The catalyst was removed by filtration through Celite and the solvent removed under vacuum. The resulting material was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/0.1% aqueous trifluoroacetic acid (60:40) to afford 64mg (90%) of the title compound as a white solid. ^{1}H NMR (200MHz,CD_3OD): 0.85 (t,7Hz,3H), 1.35 (s,3H), 1.39 (s,3H), 2.1 (m,1H), 2.3 (m,1H), 2.50-2.65 (m,4H), 3.09 (q,7Hz,2H), 4.40 (dd;6,13Hz;1H), 4.92 (d,15Hz,1H), 5.30 (d,15Hz,1H), 7.20-7.52 (m,12H). FAB-MS: calculated for $C_{31}H_{36}N_4O_3$ 512; found 514 (100%).

Example 73

N-Ethyl-4'-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)-amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from N-ethyl-4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl] [1,1'-biphenyl]-2-carboxamide, trifluoroacetate (Example 72) and D-glyceraldehyde acetonide (used crude as prepared according to the procedure of Hertel, L.W.; Grossman, C. S.; Kroin, J.S., Synth. Comm. 1991, 21, 151-154.) by the procedure described in Example 71. ^{1}H NMR (200MHz,CD_3OD): 0.87 (t,7Hz,3H), 1.35 (s,3H), 1.39 (s,3H), 2.10 (m,1H), 2.35 (m,1H), 2.50-2.65 (m,4H), 2.85-3.25 (m,4H), 3.55 (m,2H), 3.83 (m,1H), 4.40 (dd;8,12Hz;1H), 5.00 (d,15Hz,1H), 5.25 (d,15Hz,1H), 7.20-7.52 (m,12H). FAB-MS: calculated for $C_{34}H_{42}N_4O_5$ 586; found 588 (100%).

Example 74

N-(2-Hydroxyethyl)-4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

Step A: N-(2-Hydroxyethyl)-4'-[[3(R)-[[3-(benzyloxycarbonyl)amino-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide

To a solution of 70mg (0.11mmol) of 4'-[[2,3,4,5-tetrahydro-3(R)-[[3-methyl-1-oxo-3-[(benzyloxycarbonyl)amino]butyl]amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid (Example 72, Step B) in 2mL of dry methylene chloride under nitrogen at 0°C was added 0.023mL (0.17mmol) of triethylamine followed by 55mg (0.12mmol) of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate. After 5 minutes, 0.010mL (0.12mmol) of ethanolamine was added to the reaction by syringe. The reaction mixture was slowly warmed to room temperature. After 2 hours, the reaction was diluted with 75mL of ethyl acetate, washed with 25mL of 5% aqueous citric acid, 25mL of saturated sodium bicarbonate and 25mL of brine. The organic layer was dried over magnesium sulfate, filtered and the solvent removed under vacuum. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/methanol (97:3) to afford 58mg (78%) bf the product as a white foam. ^{1}H NMR (200MHz,$CDCl_3$): 1.30 (s,3H), 1.35 (s,3H), 1.80 (m,1H), 2.20-2.75 (m,7H), 3.10-3.40 (m,4H), 4.51 (m,1H), 4.92 (d,14Hz,1H), 5.00 (s,2H), 5.10 (d,14Hz,1H), 5.68 (s,1H), 6.53 (d,6Hz,1H), 7.12-7.48 (m,16H), 7.65 (d;1,6Hz;1H). FAB-MS: calculated for $C_{39}H_{42}N_4O_6$ 662; found 686 (M+Na).

Step B: N-(2-Hydroxyethyl)-4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 72, Step D. ^{1}H NMR (200MHz,CD_3OD): 1.35 (s,3H), 1.39 (s,3H), 2.00-2.40 (m,2H), 2.41-2.68 (m,4H), 3.21 (t,5Hz,2H), 3.41 (t,5Hz,2H), 4.40 (dd;6,10Hz;1H), 4.95 (d,15Hz,1H), 5.26 (d,15Hz,1H), 7.20-7.52 (m,12H). FAB-MS: calculated for $C_{31}H_{36}N_4O_4$ 528; found 530 (100%).

Example 75

N-(Phenylmethyl)-4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

Step A: N-(Phenylmethyl)-4'-[[3(R)-[[3-(benzyloxycarbonyl)amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide

The title compound was prepared from 4'-[[2,3,4,5-tetrahydro-3(R)-[[3-methyl-1-oxo-3-[(benzyloxycarbonyl)amino]butyl]amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1-biphenyl]-2-carboxylic acid (Example 72, Step B) and benzylamine according to the procedure described in Example 74, Step A. ^{1}H NMR (200MHz-,$CDCl_3$): 1.31 (s,3H), 1.35 (s,3H), 1.75 (m,1H), 2.30-2.65 (m,5H), 4.23 (d,5Hz,2H), 4.47 (m,1H), 4.83 (d,14Hz,1H), 5.02 (s,2H), 5.45 (m,1H), 5.60 (s,1H), 6.68 (d,6Hz,1H), 6.90 (m,2H), 7.10-7.50 (m,20H), 7.65 (m,1H). FAB-MS: calculated for $C_{44}H_{44}N_4O_5$ 708; found 709 (M+H), 731 (M+Na,100%).

Step B: N-(Phenylmethyl)-4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step A according to the procedure described in Example 72, Step D. ^{1}H NMR (200MHz,CD_3OD): 1.35 (s,3H), 1.39 (s,3H), 2.00-2.45 (m,2H), 2.48-2.68 (m,4H), 4.28 (m,2H), 4.40 (dd;8,12Hz;1H), 4.95 (d,15Hz,1H), 5.26 (d,15Hz,1H), 7.05 (m,2H), 7.15-7.55 (m,15H), 8.47 (t,6Hz,1H). FAB-MS: calculated for $C_{36}H_{38}N_4O_3$ 574; found 576 (100%).

Example 76

N-[(4-Methoxyphenyl)methyl]-4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1′-biphenyl]-2-carboxamide, trifluoroacetate

Step A: N-[(4-Methoxyphenyl)methyl]-4′-[[3(R)-[[3-(benzyloxycarbonyl)amino-3-methyl-1-oxo-butyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1′-biphenyl]-2-carboxamide

The title compound was prepared from 4′-[[2,3,4,5-tetrahydro-3(R)-[[3-methyl-1-oxo-3-[[(benzyloxyoxy)carbonyl]amino]butyl]amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1-biphenyl]-2-carboxylic acid (Example 72, Step B) and 4-methoxybenzylamine by the procedure described in Example 74, Step A. ^{1}H NMR (200MHz,CD_3OD): 1.40 (s,6H), 2.00 (m,1H), 2.31 (m,1H), 2.50-2.75 (m,4H), 3.82 (s,3H), 4.27 (s,2H), 4.43 (dd;7,11Hz;1H), 4.95 (d,15Hz,1H), 5.05 (d,12Hz,1H), 5.15 (d,12Hz,1H), 5.37 (d,15Hz,1H), 6.87 (m,3H), 7.03 (d,8Hz,2H), 7.20-7.57 (m,19H). FAB-MS: calculated for $C_{45}H_{46}N_4O_6$ 738; found 740.

Step B: N-[(4-Methoxyphenyl)methyl]-4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl][1,1′-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 72, Step D. ^{1}H NMR(200MHz,CD_3OD): 1.32 (s,3H), 1.37 (s,3H), 2.00-2.45 (m,2H), 2.48-2.68 (m,4H), 3.75 (s,3H), 4.20 (s,2H), 4.40 (dd;8,12Hz;1H), 4.95 (d,14Hz,1H), 5.25 (d,14Hz,1H), 6.80 (d,8Hz,2H), 6.97 (d,8Hz,2H), 7.19-7.52 (m,12H). FAB-MS: calculated for $C_{37}H_{40}N_4O_4$ 604; found 606 (100%).

Example 77

N-[(4-Hydroxyphenyl)methyl]-4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1′-biphenyl]-2-carboxamide, trifluoroacetate

To a solution of 60.5mg (0.084mmol) of N-[(4-methoxyphenyl)methyl]-4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1′-biphenyl]-2-carboxamide, trifluoroacetate (Example 76) in 3mL of dry methylene chloride under nitrogen was added 0.42mL (0.42mmol) of 1.0 M solution of boron tribromide in methylene chloride. The reaction mixture was stirred for 2 hours then 2mL of water was added followed by sufficient methanol to dissolve any remaining precipitate. The solvent was removed under vacuum. The resulting material was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/ 0.1% aqueous trifluoroacetic acid (60:40) to afford 53mg (89%) of the title compound as a white solid. ^{1}H NMR (200MHz,CD_3OD): 1.39 (s,3H), 1.45 (s,3H), 2.10-2.50 (m,2H), 2.52-2.72 (m,4H), 4.23 (s,2H), 4.48 (dd;8,12Hz;1H), 5.02 (d,14Hz,1H), 5.30 (d,14Hz,1H), 6.72 (d,8Hz,2H), 6.94 (d,8Hz,2H), 7.20-7.57 (m,12H). FAB-MS: calculated for $C_{36}H_{38}N_4O_4$ 590; found 592 (100%).

Example 78

N,N-Diethyl-4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl][1,1′-biphenyl]-2-carboxamide, trifluoroacetate

Step A: N,N-Diethyl-4′-[[3(R)-[[3-(benzyloxycarbonyl)amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1′-biphenyl]-2-carboxamide

Prepared from 4′-[[2,3,4,5-tetrahydro-3(R)-[[3-methyl-1-oxo-3-[[(benzyloxy)carbonyl]amino]butyl]-amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1′-biphenyl]-2-carboxylic acid (Example 72, Step B) and diethylamine according to the procedure described in Example 74, Step A. ^{1}H NMR (200MHz,$CDCl_3$): 0.65 (t,6Hz,3H), 0.72-1.00 (m,3H), 1.35 (s,6H), 1.96 (m,1H), 2.27 (m,1H), 2.40-2.68 (m,6H), 2.80-3.12 (m,2H), 3.55 (m,1H), 4.35 (dd;6,10Hz;1H), 4.82 (dd,6,15Hz;1H), 5.04 (dd;9,16Hz;2H), 5.40 (dd;8,14Hz;1H), 7.15-7.55 (m,17H). FAB-MS: calculated for $C_{41}H_{46}N_4O_5$ 674; found 676, 698 (M+Na).

Step B: N,N-Diethyl-4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1′-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step A by the procedure described in

Example 72, Step D. ^{1}H NMR (200MHz,CD_3OD): 0.67 (t,7Hz,3H), 0.75-1.00 (m,3H), 1.34 (s,3H), 1.39 (s,3H), 2.00-2.80 (m,7H), 2.80-3.15 (m,2H), 3.55 (m,1H), 4.40 (dd;7,12Hz;1H), 4.87 (d,15Hz,1H), 5.36 (d,15Hz,1H), 7.20-7.55 (m,12H). FAB-MS: calculated for $C_{33}H_{40}N_4O_3$ 540; found 542 (100%).

Example 79

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-1H-benzazepin-3(R)-yl]butanamide, trifluoroacetate

To a slurry of 54 mg (0.086mmol) of 4′-[[2,3,4,5-tetrahydro-3(R)-[[3-methyl-1-oxo-3-[(benzyloxycarbonyl)amino]butyl]amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1′-biphenyl]-2-carboxylic acid (Example 72, Step B) in 2mL of dry methylene chloride under nitrogen was added 0.5mL (0.5mmol) of 1.0M solution of boron tribromide in methylene chloride. The reaction mixture was stirred at room temperature for 30 minutes then quenched by the addition of 2mL of water. The remaining solids were dissolved by the addition of 2mL of methanol and the solvent were removed under vacuum. The resulting material was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/0.1% aqueous trifluoroacetic acid (60:40) to afford 38mg (74%) of the title compound as an off-white solid. ^{1}H NMR (200MHz,CD_3OD): 1.34 (s,3H),1.39(s,3H),2.00-2.46(m,2H),2.50-2.70 (m,4H),4.42 (dd;7,11Hz;1H),4.99 (d,14Hz,1H),5.23 (d,14Hz, 1H),7.2-7.6(m,11H),7.76(dd;1,7Hz;1H). FAB-MS: calculated for $C_{29}H_{31}N_3O_4$ 485; found 486 (M+H,100%).

Example 80

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-hydroxymethyl[1,1′-biphenyl]-4-yl]methyl]-1H-benzazepin-3(R)-yl]butanamide, trifluoroacetate

Step A: 3-[(Benzyloxycarbonyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-hydroxymethyl[1,1′-biphenyl]-4-yl]methyl]-1H-benzazepin-3(R)-yl]butanamide

To a solution of 124mg (0.20mmol) of 4′-[[2,3,4,5-tetrahydro-3(R)-[[3-methyl-1-oxo-3-[(benzyloxycarbonyl)amino]butyl]amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1′-biphenyl]-2-carboxylic acid (Example 72, Step B) in 1.5mL of dry 1,2-dimethoxyethane at 0°C was added 0.046mL (0.421mmol) of N-methylmorpholine followed by 0.055mL (0.42mmol) of isobutyl chloroformate. The reaction mixture was stirred at 0°C for 1 hour then filtered. Solids were rinsed with 1,2-dimethoxyethane (2x1mL) and the filtrates combined. To the filtrate at 0°C was added by syringe a solution of 30.3mg (0.801mmol) of sodium borohydride in 0.3mL of water. The reaction mixture was stirred at 0°C for 15 minutes then diluted with ethyl acetate (75mL). The organic layer was washed with saturated aqueous ammonium chloride (25mL) and brine (25mL), then dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/hexane (75:25) to afford 86mg (71%) of the product as a white solid. ^{1}H NMR (200MHz,$CDCl_3$): 1.35 (s,3H), 1.37 (s,3H), 2.80 (m,2H), 2.50 (m,4H), 4.50 (m,3H), 4.90 (d,15Hz,1H), 5.03 (dd;10,12Hz;2H), 5.18 (d,15Hz,1H), 5.77 (s,1H), 6.70 (d,8Hz,1H), 7.10-7.40 (m,16H), 7.53 (m,1H). FAB-MS: calculated for $C_{37}H_{39}N_3O_5$ 605; found 607 (30%).

Step B: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-hydroxymethyl[1,1′-biphenyl]-4- yl]methyl]-1H-benzazepin-3(R)-yl]butanamide, trifluoroacetate

To a solution of 40mg (0.066mmol) of the intermediate obtained in Step A in 2mL of methanol was added 5mg of 20% palladium hydroxide on carbon catalyst. The resulting mixture was hydrogenated at room temperature and 1 atmosphere for 30 minutes. The catalyst was removed by filtration through Celite and the solvent removed under vacuum. The residue was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/ 0.1% aqueous trifluoroacetic acid (60:40) to afford 36mg (95%) of the title compound as a white solid. ^{1}H NMR (200MHz,CD_3OD): 1.34 (s,3H), 1.37 (s,3H), 2.0-2.7 (m,6H), 4.44 (m,3H), 4.95 (d,15Hz,1H), 5.25 (d,15Hz,1H), 7.1-7.5 (m,11H), 7.55 (d,6Hz,1H). FAB-MS: calculated for $C_{29}H_{33}N_3O_3$ 471; found 472 (M+H,100%).

Example 81

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-methyl[1,1'-biphenyl]-4-yl]methyl]-1H-benzazepin-3(R)-yl]butanamide, trifluoroacetate

To a solution of 30mg (0.066mmol) of 3-[(benzyloxycarbonyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-benzazepin-3(R)-yl]butanamide (Example 80, Step A) in 2mL of methanol was added 5mg of 20% palladium hydroxide on carbon catalyst and 1 drop of trifluoroacetic acid. The resulting mixture was hydrogenated at room temperature and 1 atmosphere for 4 hours. The catalyst was removed by filtration through Celite and the solvent removed under vacuum. The residue was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/ 0.1% aqueous trifluoroacetic acid (65:35) to afford 30mg (100%) of the title compound as a white solid. ^{1}H NMR (200MHz,CD_3OD): 1.35 (s,3H), 1.40 (s,3H), 2.0- 2.7 (m,6H), 2.10 (s,3H), 4.42 (dd;8,12Hz;1H), 4.95 (d,14Hz,1H), 5.27 (d,14Hz,1H), 7.1-7.4 (m,12H). FAB-MS: calculated for $C_{29}H_{33}N_3O_2$ 455; found 456 (M+H,100%).

Example 82

4'-[[3(R)-[[3-[(2(S),3(S),4-Trihydroxybutylamino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

Step A: 1-t-Butyldimethylsilyl-2,3-isopropylidene-D-threitol

To a solution of 1.0g (6.2mmol) of 2,3-isopropylidene-D-threitol in 6.0mL of dry dimethylformamide at 0°C was added 0.44g (6.5mmol) of imidazole followed by dropwise addition of a solution of 0.93g (6.2mmol) of t-butyldimethylsilyl chloride in 6.0mL of dimethylformamide. The reaction mixture was stirred at 0°C for 30 minutes then at room temperature for 1 hour. The reaction mixture was poured into 75mL water and extracted with ether (3x75mL). The combined ether extracts were washed with saturated aqueous sodium bicarbonate and with brine. The organic layer was dried over magnesium sulfate, filtered and the solvent removed undervacuum. The resulting oil was purified by flash chromatography on silica gel, eluting with hexanes/ethyl acetate (75:25) to afford 0.70g (41%) of product as a clear oil. ^{1}H NMR (200Mhz,$CDCl_3$): 0.07 (s,6H), 0.90 (s,9H), 1.39 (s,3H), 1.41 (s,3H), 3.60-4.00 (m,7H). FAB-MS: calculated for $C_{13}H_{28}O_4Si$ 276; found 261 (M-15,10%).

Step B: 5(S)-t-Butyldimethylsilyloxymethyl-2,2-dimethyl-1,3-dioxolan-4(R)-carboxaldehyde

To a solution of 0.676g (2.44mmol) of the intermediate obtained in Step A in 35mL of dry methylene chloride was added 3mL of dry dimethylsulfoxide followed by 2.8mL (20.2mmol) of triethylamine. To this solution was added 1.61g (10.1mmol) of pyridine sulfur trioxide complex in three portions over a 5 minute period. The reaction mixture was stirred at room temperature for 2 hours at which time it was diluted with 250mL of ethyl acetate. The mixture was transferred to a separatory funnel and washed with 1N HCl (2x50mL), saturated aqueous sodium bicarbonate (50mL) and brine (50mL). The organic layer was dried over magnesium sulfate, filtered, and the solvent removed under vacuum to afford 672mg (100%) of product which was used in the next reaction without further purification. ^{1}H NMR (200MHz,$CDCl_3$): 0.09 (s,6H), 0.87 (s,9H), 1.40 (s,3H), 1.45 (s,3H), 3.78 (d,4Hz,2H), 4.10 (m,1H), 4.30 (dd;2,6Hz;1H), 9.85 (d,2Hz,1H).

Step C: 4'-[[3(R)-[[3-[(2(S),3(S),4-Trihydroxybutylamino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from 4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide, trifluoroacetate (Example 69) and the intermediate obtained in Step B by the procedure described in Example 71. ^{1}H NMR (200MHz,CD_3OD): 1.37 (s,3H), 1.41 (s,3H), 2.12-2.40 (m,2H), 2.55-2.71 (m,4H), 3.05-3.25 (m,2H), 3.59 (m,3H), 3.92 (m,1H), 4.40 (dd;7,12Hz;1H), 5.02 (d,15Hz,1H), 5.15 (d,15Hz,1H), 7.20-7.58 (m,12H). FAB-MS: calculated for $C_{33}H_{40}N_4O_6$ 588; found 589 (M+H,70%).

Example 83

4'-[[3(R)-[(2(R)-amino-3-hydroxy-1-oxopropyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide, trifluoroacetate

Step A: 2(R)-t-Butoxycarbonylamino-3-(t-butoxy)-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]propanamide

To a solution of 200mg (1.13mmol) of 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin -2-one (Example 1, Step B) in 8mL of dry methylene chloride was added 0.206mL (1.48mmol) of triethylamine, 553mg (1.25mmol) of BOC-D-serine t-butyl ether followed by 602mg (1.36mmol) of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate. The reaction mixture was stirred at room temperature for 2 hours then diluted with 100mL of ethyl acetate, washed with 25mL of 5% aqueous citric acid, 25mL of saturated sodium bicarbonate and 25mL of brine. The organic layer was dried over magnesium sulfate, filtered and the solvents removed under vacuum. the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexane (55:45) to afford 480mg (100%) of the product as a white foam. ^{1}H NMR (200MHz,$CDCl_3$): 1.20 (s,9H), 1.47 (s,9H), 1.92 (m,1H), 2.55-3.02 (m,3H), 3.38 (t,8Hz,1H), 3.78 (m,1H), 4.15 (m,1H), 4.52 (m,1H), 5.45 (s,1H), 7.00 (m,1H), 7.10-7.35 (m,3H), 7.68 (d,4Hz,1H), 8.05 (s,1H). FAB-MS: calculated for $C_{22}H_{33}N_3O_5$ 419; found 420 (M+H,20%), 426 (M+Li,40%).

Step B: 2(R)-t-Butoxycarbonylamino-3-(t-butoxy)-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-cyano[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]propanamide

Prepared from the intermediate obtained in Step A and 4'-bromomethyl-1,1'-biphenyl-2-nitrile (Example 69, Step C) by the procedure described in Example 69, Step D. ^{1}H NMR (200MHz,$CDCl_3$): 1.20 (s,9H), 1.47 (s,9H), 1.88 (m,1H), 2.45-2.75 (m,3H), 3.38 (dd;6,8Hz;1H), 3.78 (m,1H), 4.15 (m,1H), 4.52 (m,1H), 4.97 (d,14Hz,1H), 5.21 (d,14Hz,1H), 5.40 (s,1H), 7.1-7.5 (m,11H), 7.6-7.8 (m,2H). FAB-MS: calculated for $C_{36}H_{42}N_4O_5$ 610; found 618 (M+Li,30%).

Step C: 4'-[[3(R)-[[2(R)-(t-Butoxycarbonyl)amino-3-hydroxy-1-oxopropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide

Prepared from the intermediate obtained in Step B by the procedure described in Example 69, Step E. ^{1}H NMR (400MHz,$CDCl_3$): 1.18 (s,9H), 1.45 (s,9H), 1.85 (m,1H), 2.45 (m,1H), 2.62 (m,2H), 3.38 (dd;6,8Hz;1H), 3.72 (m,1H), 4.12 (m,1H), 4.47 (m,1H), 4.92 (d,14Hz,1H), 5.13 (s,1H), 5.20 (d,14Hz,1H), 5.37 (s,2H), 7.17 (m,3H), 7.2-7.4 (m,6H), 7.40 (m,1H), 7.47 (m,1H), 7.60 (s,1H), 7.72 (d,8Hz,1H). FAB-MS: calculated for $C_{36}H_{44}N_4O_6$ 628; found 636 (M+Li,40%).

Step D: 4'-[[3(R)-[(2(R)-Amino-3-hydroxy-1-oxopropyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 69, Step F. ^{1}H NMR (200MHz,CD_3OD): 2.10 (m,1H), 2.37 (m,1H), 2.62 (m,2H), 3.8-4.1 (m,3H), 4.42 (dd;6,11Hz;1H), 4.95 (d,14Hz,1H), 5.27 (d,14Hz,1H), 7.2-7.6 (m,12H). FAB-MS: calculated for $C_{27}H_{28}N_4O_4$ 472; found 473 (M+H,100%).

Example 84

4'-[[3(R)-[(2-Amino-2-methyl-1-oxopropyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1.1'-biphenyl]-2-carboxamide, trifluoroacetate

Step A: 2-t-Butoxycarbonylamino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-cyanol[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide

Prepared from 2-t-butoxycarbonylamino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]propanamide (Example 63, Step A) and 4'-bromomethyl-1-1'-biphenyl-2-nitrile (Example 69, Step C) by the procedure described in Example 69, Step D. ^{1}H NMR (200MHz,$CDCl_3$): 1.39 (s,9H), 1.41 (s,3H), 1.45 (s,3H), 1.83 (m,1H), 2.4-2.8 (m,3H), 4.48 (m,1H), 4.90 (d,16Hz,1H), 4.93 (s,1H), 5.22 (d,16Hz,1H), 7.1-7.5 (m,10H),

7.60 (m,1H), 7.72 (d,6Hz,1H). FAB-MS: calculated for $C_{33}H_{36}N_4O_4$ 552; found 554 (20%).

Step B: 4'-[[3(R)-[[2-(t-Butoxycarbonyl)amino-2-methyl-1-oxopropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide

Prepared from the intermediate obtained in Step A by the procedure described in Example 69, Step E. ^{1}H NMR (200MHz,$CDCl_3$): 1.40 (s,12H), 1.43 (s,3H), 1.83 (m,1H), 2.4-2.8 (m,3H), 4.48 (m,1H), 4.85 (d,14Hz,1H), 4.97 (s,1H), 5.20 (s,1H), 5.22 (d,14Hz,1H), 5.57 (s,1H), 7.1-7.5 (m,11H), 7.70 (dd;1,6Hz;1H).

Step C: 4'-[[3(R)-[(2-Amino-2-methyl-1-oxopropyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 69, Step F. ^{1}H NMR (200MHz,CD_3OD): 1.52 (s,3H), 1.65 (s,3H), 2.25 (m,2H), 2.60 (m,2H), 4.40 (m,1H), 5.00 (d,7Hz,1H), 5.20 (d,7Hz,1H), 7.2-7.6 (m,12H). FAB-MS: calculated for $C_{28}H_{30}N_4O_3$ 470; found 471 (M+H,100%)

Example 85

3-(2-Aminoethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-carboxy[1,1'-biphenyl]-4-yl]methyl]-1H-benzazepin-3(R)-yl]butanamide, dihydrochloride

Step A: 4'-[[2,3,4,5-Tetrahydro-3(R)-[[3-methyl-1-oxo-3-amino]butyl]amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid, 1,1-dimethylethyl ester, acetate

To a solution of 400mg (0.592mmol) of 4'-[(2,3,4,5-tetrahydro-3(R)-[[3-methyl-1-oxo-3-[(benzyloxycarbonyl)amino]butyl]amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid 1,1-dimethylethyl ester (Example 72, Step A) in 10mL of methanol was added 0.034mL (0.59mmol) of acetic acid and 80mg of 20% palladium hydroxide on carbon catalyst. The resulting mixture was hydrogenated at room temperature and 1 atmosphere for 4 hours. The catalyst was removed by filtration through Celite and the filtrate concentrated under vacuum to afford 345mg (97%) of the product as a white solid. ^{1}H NMR (400MHz,CD_3OD): 1.17 (s,9H), 1.35 (s,3H), 1.42 (s,3H), 1.95 (s,3H), 2.15 (m,1H), 2.35 (m,1H), 2.50 (d,12Hz,1H), 2.5-2.78 (m,3H), 4.42 (dd;8,11Hz;1H), 5.02 (d,15Hz,1H), 5.37 (d,15Hz,1H), 7.1-7.6 (m,11H), 7.67 (d,8Hz,1H). FAB-MS: calculated for $C_{33}H_{39}N_3O_4$ 541; found 542 (M+H,100%).

Step B: 2-(t-Butoxycarbonylamino)acetaldehyde

To a solution of 700mg (4.34mmol) of 2-(t-butoxycarbonylamino)ethanol in 35mL of dry methylene chloride was added 4.0mL of dimethylsulfoxide and 4.8mL (35mmol) of triethylamine, followed by 2.8g (17mmol) of pyridine sulfur trioxide complex in three portions over 5 minutes. The reaction was stirred at room temperature for 3 hours then diluted with 500mL of ether. The mixture was transferred to a separatory funnel and washed with 1NHCl (2x50mL), saturated aqueous sodium bicarbonate (100mL), and brine (100mL). The organic layer was dried over magnesium sulfate, filtered, and the solvent removed under vacuum to afford 550mg (80%) of product which was used without further purification. ^{1}H NMR (200MHz,$CDCl_3$): 1.40 (s,9H), 4.05 (d,7Hz,2H), 5.17 (s,1H), 9.62 (s,1H).

Step C: 3-(2-Aminoethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-carboxy-[1,1'-biphenyl]-4-yl)methyl]-1H-benzazepin-3(R)-yl]butanamide, dihydrochloride

To a solution of 345mg (0.573mmol) of the intermediate obtained in Step A in 10mL of dry methanol was added 0.088mL (0.63mmol) of triethylamine, 3.4g of dry 4A powdered molecular sieves followed by a solution of 540mg (3.4mmol) of 2-(t-butoxycarbonylamino)acetaldehyde (Step B) in 5mL of dry methanol. The pH of the mixture was carefully adjusted to 6.5 with glacial acetic acid (7 drops). The reaction was stirred for 3 hours at which time 3.4mL (3.4mmol) of a 1.0 M solution of sodium cyanoborohydride in tetrahydrofuran was added by syringe. The reaction was stirred for 20 hours then filtered through a pad of Celite. To the filtrate was added 2.0mL of acetic acid (CAUTION! evolution of hydrogen cyanide). The resulting mixture was stirred for 3 hours. The solvent was removed under vacuum to afford a clear oil which was dissolved in 5mL of methylene chloride. To this solution was added 5 drops of anisole followed by 5mL of trifluoroacetic acid. The mixture was stirred

for 4 hours at room temperature then all volatiles removed under vacuum to give an oil which was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/0.1% aqueous trifluoroacetic acid (55:45). The product thus obtained was converted to its dihydrochloride salt by dissolving it in 10mL of 6 N HCl followed by evaporation under vacuum. The cycle was repeated three times to afford 273mg (79%) of the title compound as an off-white solid. ^{1}H NMR (200MHz,CD_3OD): 1.45 (s,3H), 1.51 (s,3H), 2.1-2.5 (m,2H), 2.5-2.7 (m,4H), 3.2-3.5 (m,4H), 4.42 (dd;8,11Hz;1H), 5.00 (d,15Hz,1H), 5.22 (d,15Hz,1H), 7.2-7.6 (m,11H), 7.78 (d,6Hz,1H). FAB-MS: calculated for $C_{31}H_{36}N_4O_4$ 528; found 529 (M+H,100%).

Example 86

3-[(2(S)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 3-[(2-(S)-Benzyloxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

To a solution of 0.20g (0.34mmol) of 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 1) in 8mL of dry methanol was added 0.096mL (2.50mmol) of triethylamine, 1.0g of dry 4A powdered molecular sieves followed by a solution of 0.296g (1.80mmol) of (S)-2-benzyloxypropanal (prepared from ethyl-L-lactate according to the procedure of Hanessian and Kloss, Tetrahedron Lett. 1985, 26, 1261-1264.) in 2mL of dry methanol. The pH of the mixture was carefully adjusted to 6.5 with glacial acetic acid. The reaction was stirred for 2 hours at which time 2.06mL (2.06mmol) of a 1.0 M solution of sodium cyanoborohydride in tetrahydrofuran was added by syringe. The reaction was stirred for 24 hours then filtered through a pad of Celite. To the filtrate was added 5.0mL of trifluoroacetic acid (CAUTION! evolution of hydrogen cyanide) and the resulting mixture was stirred for three hours. The solvent was removed under vacuum to afford 1.6g of a clear oil which was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/0.1% aqueous trifluoroacetic acid (65:35) to afford 254mg (100%) of the product as a white solid. ^{1}H NMR (200MHz,CD_3OD): 1.28 (d,6Hz,3H), 1.35 (s,3H), 1.40 (s,3H), 2.10 (m,1H), 2.2-2.7 (m,5H), 2.95 (m,1H), 3.20 (m,1H), 3.83 (m,1H), 4.42 (m,1H), 4.50 (d,11Hz,1H), 4.63 (d,11Hz,1H), 5.20 (d,15Hz,1H), 6.95 (d,8Hz,2H), 7.1-7.7 (m,15H). FAB-MS: calculated for $C_{39}H_{43}N_7O_3$ 657; found 658 (M+H,100%).

Step B: 3-[(2(S)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

A solution of 250mg (0.324mmol) of the intermediate prepared in Step A in 5mL of methanol was placed in a shaker bottle. To the solution was added 3 drops of trifluoroacetic acid and 0.1g of 30% palladium on carbon. The mixture was hydrogenated at room temperature and 40psi for 3 days. The catalyst was removed by filtration through Celite and the filtrate evaporated under vacuum. The resulting material was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/0.1% aqueous trifluoroacetic acid (60:40) to afford 149mg (64%, Steps A + B) of the title compound as a white solid. ^{1}H NMR (200MHz,CD_3OD): 1.20 (d,6Hz,3H), 1.35 (s,3H), 1.40 (s,3H), 2.10 (m,1H), 2.2-2.6 (m,5H), 2.78 (m,1H), 3.08 (m,1H), 3.92 (m,1H), 4.35 (dd;7,10Hz;1H), 4.95 (d,14Hz,1H), 5.18 (d,14Hz,1H), 7.00 (d,8Hz,2H), 7.1-7.4 (m,6H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{32}H_{37}N_7O_3$ 567; found 568 (M+H,100%).

Example 87

3-[[2-(t-Butoxycarbonylamino)ethyl]amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide. trifluoroacetate

To a solution of 485mg (0.833mmol) of 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 1) in 8mL of dry methanol was added 0.232mL (1.67mmol) of triethylamine, 2.5g of dry 4A powdered molecular sieves followed by a solution of 200mg (1.25mmol) of 2-(t-butoxycarbonylamino)acetaldehyde (Example 85, Step B) in 1mL of dry methanol. The pH of the mixture was carefully adjusted to 6.5 with glacial acetic acid. The reaction was stirred for 2 hours at which time 5.0mL (5.0mmol) of a 1.0 M solution of sodium cyanoborohydride in tetrahydrofuran was added by syringe. The reaction was stirred for 20 hours then filtered through a pad of Celite. To the filtrate was added 1.0mL of acetic acid (CAUTION: evolution of hydrogen cyanide). The resulting mixture

was stirred for 30 minutes. The solvent was removed under vacuum to afford a clear oil which was purified by reverse phase high pressure liquid chromatography on C-18 eluting with methanol/0.1% aqueous trifluoroacetic acid (65:35) to afford 347mg (54%) of the title compound as a white solid. ^{1}H NMR (200MHz,CD_3OD): 1.30 (s,9H), 1.35 (s,3H), 1.39 (s,3H), 2.10 (m,1H), 2.2-2.6 (m,5H), 3.10 (m,2H), 3.35 (m,2H), 4.39 (dd;8,11Hz;1H), 4.95 (d,15Hz,1H), 5.21 (d,15Hz,1H), 7.05 (m,2H), 7.2-7.5 (m,7H), 7.5-7.7 (m,3H). FAB-MS: calculated for $C_{36}H_{44}N_8O_4$ 652; found 654 (100%).

Example 88

3-[(2-Aminoethyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, di(trifluoroacetate)

The title compound was prepared from 3-[[(2-t-butoxycarbonylamino)ethyl]amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, monotrifluoroacetate (Example 87) by the procedure described in Example 69, Step F. ^{1}H NMR (200MHz,CD_3OD): 1.38 (s,3H), 1.42 (s,3H), 2.12 (m,1H), 2.2-2.7 (m,5H), 3.33 (m,4H), 4.35 (dd;6,11Hz;1H), 4.85 (d,15Hz,1H), 5.21 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.1-7.4 (m,7H), 7.5-7.7 (m,3H). FAB-MS: calculated for $C_{31}H_{36}N_8O_2$ 552; found 553 (M+H,100%).

Example 89

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[1-(carboxymethyl)tetrazol-5-yl][1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 3-(t-Butoxycarbonylamino)-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[1-(carboxymethyl)tetrazol-5-yl](1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, t-butyl ester and, 3-(t-Butoxycarbonylamino)-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[2-(carboxymethyl)tetrazol-5-yl][1,1'biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, t-butyl ester

To a solution of 101mg (0.166mmol) of 3-(t-butoxycarbonylamino)-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide (Example 16, Step A) in 1mL of acetone was added 0.028mL (0.20mmol) of triethylamine followed by dropwise addition of 0.029mL (0.18mmol) of t-butyl bromoacetate. The reaction mixture was stirred at room temperature for 1 hour then the solvent was removed under vacuum. The residue was dissolved in 50mL of methylene chloride, washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate and filtered. The filtrate was evaporated under vacuum to afford 139mg (100°%) of product as a mixture of N-1 and N-2 tetrazole isomers. ^{1}H NMR of mixture (200MHz,$CDCl_3$): 1.30 (s,6H), 1.40 (s,6H), 1.50 (m,36H), 1.90 (m,2H), 2.4-2.7 (m,8H), 3.80 (s,2H), 4.07 (s,2H), 4.52 (m,2H), 4.80 (m,2H), 5,37 (m,2H), 6.72 (m,2H), 7-.0-7.4 (m,16H), 7.4-7.8 (m,6H). FAB-MS calculated for $C_{40}H_{49}N_7O_6$ 723; found 724 (M+H,20%).

Step B: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[1-(carboxymethyl)tetrazol-5-yl]-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Prepared from the intermediate obtained in Step A by the procedure described in Example 69, Step F. Separation of isomers by reverse phase high pressure liquid chromatography on C-18 eluting with methanol/0.1% aqueous trifluoroacetic acid afforded the title compound in addition to the N-2 isomer. ^{1}H NMR (200MHz,CD_3OD): 1.39 (s,3H), 1.42 (s,3H), 2.0-2.7 (m,6H), 4.40 (dd;8,11Hz;1H), 4.48 (s,2H), 4.85 (d,15Hz,1H), 5.35 (d,15Hz,1H), 7.05 (d,8Hz,2H), 7.2-7.4 (m,7H), 7.5-7.9 (m,3H). FAB-MS: calculated for $C_{31}H_{33}N_7O_44$ 567; found 568 (M+H,100%).

Example 90

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[2-(carboxymethyl)tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from 3-(t-butoxycarbonylamino)-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[2-(carboxymethyl)-tetrazol-5-yl]-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, t-butyl ester (Example 89, Step A) by the procedure described in Example 89, Step B. ^{1}H NMR (200MHz,CD_3OD):

1.35 (s,3H), 1.42 (s,3H), 2.0-2.6 (m,6H), 4.39 (dd;7,11Hz;1H), 4.90 (d,14Hz,1H), 5.20 (d,14Hz,1H), 5.42 (s,2H), 7.04 (d,6Hz,2H), 7.15 (d,6Hz,2H), 7.2-7.6 (m,7H), 7.75 (m,1H). FAB-MS: calculated for $C_{31}H_{33}N_7O_4$ 567; found 568 (M+H,100%).

Example 91

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2,5-dioxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide trifluoroacetate

Step A: 3-t-Butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2,5-dioxo-1H-1-benzazepin-3-yl]-butanamide

To a solution of 120mg (0.531mmol) of 3-t-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1-benzazepin-2,5-dione (prepared by the procedure of F. Stewart, australian J. Chem. 1980, 33, 633-640.) in 2mL of methanol was added 2mL of 9 N hydrochloric acid. The mixture was stirred at room temperature for 24 hours and solvent was removed under vacuum.

To the resulting solid in 3mL of dry methylene chloride was added 0.22mL (1.6mmol) of triethylamine, 115mg (0.531mmol) of 3-t-butoxycarbonylamino-3-methyl butanoic acid (Example 31, Step E) followed by 235mg (0.531mmol) of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate. The reaction mixture was stirred at room temperature for 2 hours. The reaction was diluted with 75mL of ethyl acetate, washed with 25mL of 5% aqueous citric acid, 25mL of saturated aqueous sodium bicarbonate and 25mL of brine. The organic layer was dried over magnesium sulfate, filtered and the solvent removed under vacuum. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/hexanes (65:35) to afford 109mg (51%) of the product as a white foam. ^{1}H NMR (200MHz,$CDCl_3$): 1.33 (s,3H), 1.39 (s,12H), 2.49 (d,12Hz,1H), 2.75 (d,12Hz,1H), 2.9 (m,1H), 3.27 (dd;2,16Hz; 1H), 5.05 (m,2H), 7.05 (t,6Hz,1H), 7.24 (t,6Hz,1H), 7.50 (m,1H), 7.82 (dd;2,8Hz;1H), 8.85 (s,1H). FAB-MS: calculated for $C_{20}H_{27}N_3O_5$ 389; found 390 (M+H,60%).

Step B: 3-(t-Butoxycarbonylamino)-3-methyl-N-(2,3,4,5-tetrahydro-2,5-dioxo-1-[[2'-(N-triphenylmethyl)tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole (Example 1, Step J) by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz,$CDCl_3$): 1.35 (s,3H), 1.40 (s,12H), 2.49 (d,14Hz,1H), 2.6-2.9 (m,2H), 3.27 (m,1H), 4.82 (d,15Hz,1H), 4.92 (d,15Hz,1H), 5.05 (s,1H), 5.15 (m,1H), 6.8-7.6 (m,26H), 7.90 (m,1H). FAB-MS: calculated for $C_{53}H_{51}N_7O_5$ 865; found 873 (M+Li).

Step C: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2,5-dioxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

To a solution of 68mg (0.078mmol) of the intermediate obtained in Step B in 3mL of methanol was added 14mg of palladium hydroxide catalyst. The mixture was hydrogenated at room temperature and 1 atmosphere for 20 hours at which time the solids were filtered and the solvent removed under vacuum.

The resulting solid was dissolved in 3mL of methylene chloride. To this solution was added 3 drops of anisole followed by 2mL of trifluoroacetic acid. The reaction mixture was stirred for 2 hours at room temperature, then all volatiles removed under vacuum. The resulting material was purified by reverse phase high pressure liquid chromatography on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient; 50% methanol increased to 55% methanol over 12 minutes) to afford 16.5mg (33%) of the title compound as a white solid. ^{1}H NMR (200MHz,CD_3OD): 1.37 (s,3H), 1.40 (s,3H), 2.59 (dd;14,16Hz;2H), 2.9-3.2 (m,2H), 4.97 (d,15Hz,1H), 5.17 (dd;4,12Hz;1H), 5.25 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.12 (d,8Hz,2H), 7.37 (m,2H), 7.4-7.7 (m,6H). FAB-MS: calculated for $C_{29}H_{29}N_7O_33$ 523; found 524 (M+H,100%).

Example 92

3-Amino-3-methyl-N-[5-hydroxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

To a solution of 23mg (0.036mmol) of 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2,5-dioxo-1-[[2'-(1H-tetra-

zol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate (Example 91) in 1mL of methanol/water (4:1) was added 14mg (0.36mmol) of sodium borohydride. The reaction mixture was stirred for 1 hour then quenched by the addition of 5 drops of trifluoroacetic acid. The solvent was removed under vacuum and the resulting material was purified by reverse phase high pressure liquid chromatography on C-18 eluting with methanol/0.1% aqueous trifluoroacetic acid (55:45) to afford 18mg (78%) of the title compound as a white solid. ^{1}H NMR (200MHz, CD_3OD): 1.37 (s,3H), 1.40 (s,3H), 2.17 (m,1H), 2.3-2.6 (m,3H), 4.30 (dd;8,10Hz;1H), 4.67 (dd;6,10Hz;1H), 4.95 (d,15Hz,1H), 5.23 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.20 (d,8Hz,2H), 7.35 (m,3H), 7.5-7.7 (m,5H). FAB-MS: calculated for $C_{29}H_{31}N_7O_4$ 525; found 526 (M+H,100%).

Example 93

4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-thioamide, trifluoroacetate

Step A: 4-[[3(R)-[(3-t-Butoxycarbonylamino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-thioamide

A solution of 380mg (0.67mmol) of 3-[[1-[[2-cyano-[1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepin-3(R)-yl]amino]-1,1-dimethyl-3-oxopropylcarbamic acid, 1,1-dimethylethyl ester (Example 69, Step D), in 5mL of pyridine was placed in a bomb and treated with 5mL of triethylamine and excess hydrogen sulfide was introduced under pressure. The bomb was sealed and heated for 12 hours at 90°C. The bomb was vented into 5 M sodium hydroxide and the contents poured into 40mL of water, then extracted with ether (3x). The combined extracts were washed with water (3x), dried over magnesium sulfate, filtered and evaporated under vacuum to afford 330mg (0.53mmol, 82%) of product. ^{1}H NMR (200MHz, $CDCl_3$): 1.38 (s,6H), 1.45 (s,9H), 1.90 (m,1H), 2.4-2.7 (m,4H), 2.92 (m,1H), 4.55 (m,1H), 6.50 (br s,1H), 6.70 (m,1H), 7.1-7.5 (m,12H), 7.82 (m,1H). FAB-MS (Li+ spike): calculated for $C_{34}H_{40}N_4O_4S$ 600; found 607 (M+Li, 65%).

Step B: 4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-thiomide, trifluoroacetate

A suspension of 80mg (0.13mmol) of the intermediate prepared in Step A in 10mL of methylene chloride at room temperature was treated with 5mL of trifluoroacetic acid. After 45 minutes, all volatiles were removed under vacuum and the residue placed under high vacuum. Purification by preparative thin layer chromatography on a 1mm silica plate eluting with methylene chloride/methanol/acetic acid (9:1:0.1) afforded 43mg of the free amine which was converted to the trifluoroacetate salt by dissolving in 3mL of methanol and adding 0.5mL of trifluoroacetic acid, followed by removal of volatiles under vacuum. In this manner, 30mg (0.05mmol, 37%) of the title compound was obtained. ^{1}H NMR (400MHz, CD_3OD): 1.35 (s,3H), 1.39 (s,3H), 2.11 (m,1H), 2.31 (m,1H), 2.45-2.65 (m,4H), 4.40 (dd;7,11Hz;1H), 4.94 (d,15Hz,1H), 5.24 (d,15Hz,1H), 7.20-7.55 (m,12H). FAB-MS:calculated for $C_{29}H_{32}N_4O_2S$ 500; found 501 (M+H,100%).

Example 94

N-Hydroxy-4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)-amino]2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl]-[1,1'-biphenyl]-2-carboxamide, trifluoro-acetate

Step A: N-Hydroxy-4'-[[2,3,4,5-Tetrahydro-3(R)-[[3-methyl-1-oxo-3-[[(benzyloxy)carbonyl]amino]-butyl]-amino]-2-oxo-1H-1-benzazepin-1-yl]-methyl][1,1'-biphenyl]-2-carboxamide

Prepared from 4'-[[2,3,4,5-Tetrahydro-3(R)- [[3-methyl-1-oxo-3-[[(benzyloxy)carbonyl]amino]butyl]-amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid (Example 72, Step B) and (O-trimethylsilyl)hydroxylamine by the procedure described in Example 72, Step C. ^{1}H NMR (200MHz,$CDCl_3$): 1.33 (s,3H), 1.36 (s,3H), 1.77 (m,1H), 2.3-2.5 (m,4H), 4.46 (m,1H), 4.68 (d,15Hz,1H), 5.02 (s,2H), 5.14 (d,15Hz,1H), 5.73 (br s,1H), 6.82 (d,7Hz,1H), 7.1-7.5 (m,16H), 7.60 (d,8Hz,1H). FAB-MS: calc. for $C_{37}H_{38}N_4O_5$ 634; found 635 (M+H,1%).

Step B: N-Hydroxy-4'-[[3(R)-[(3-amino-3-methyl-1-oxo-butyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 79. ^{1}H NMR (200MHz, CD_3OD): 1.36 (s,3H), 1.39 (s,3H), 2.0-2.7 (m,6H), 4.41 (dd;7,11Hz;1H), 5.03 (d,15Hz,1H), 5.18 (d,15Hz), 7.2-7.6 (m,12H). FAB-MS: calculated for $C_{29}H_{32}N_4O_4$ 500; found 502 (100%).

Example 95

4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-nitro-1,1'-biphenyl, trifluoroacetate

Step A: 4'-Methyl-2-nitro-1,1'-biphenyl

Prepared from 4-methylphenyltrimethylstannane (Example 69, Step A) and 2-bromonitrobenzene by the procedure described in Example 69, Step B. ^{1}H NMR (200MHz,$CDCl_3$): 2.39 (s,3H), 7.23 (m,3H), 7.45 (m,3H), 7.58 (t,7Hz,1H), 7.80 (d,7Hz,1H).

Step B: 4'-Bromomethyl-2-nitro-1-1'-biphenyl

Prepared from 4'-methyl-2-nitro-1,1'- biphenyl by the procedure described in Example 69, Step C. ^{1}H NMR (200MHz,$CDCl_3$): 4.53 (s,2H), 7.2-7.7 (m,7H), 7.85 (m,1H). FAB-MS: calculated for $C_{14}H_{10}BrN$ 272; found 272,274 (M+). ^{1}H NMR indicates the presence of minor amounts of starting material and dibromo derivative.

Step C: 3-[[1-[[2'-Nitro-[1,1'-biphenyl]-4-yl]-methyl]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepin-3(R)-yl]amino]-1,1-dimethyl-3-oxopropyl]carbamic acid, 1,1-dimethylethyl ester

Prepared from 4'-bromomethyl-2-nitro-1,1'-biphenyl and 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) by the procedure described in Example 69, Step D. ^{1}H NMR (200MHz, $CDCl_3$): 1.34 (s,6H), 1.41 (s,9H), 1.83 (m,1H), 2.35-2.70 (m,5H), 4.50 (m,1H), 4.84 (d,15Hz,1H), 5.23 (d,15Hz,1H), 5.27 (s,1H), 6.64 (d,7Hz,1H), 7.1-7.6 (m,11H), 7.80 (d,8Hz,1H).

Step D: 4'[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-nitro-1-1'-biphenyl, trifluoroacetate

Prepared from the intermediate obtaired in Step C by the procedure described in Example 69, Step F. ^{1}H NMR (400MHz,CD_3OD): 1.34 (s,3H), 1.38 (s,3H), 2.11 (m,1H), 2.32 (m,1H), 2.4-2.7 (m,4H), 4.40 (dd;8,11Hz;1H), 4.99 (d,15Hz,1H), 5.21 (d,15Hz,1H), 7.1-7.4 (m,8H), 7.45 (d,8Hz,1H), 7.54 (t,8Hz,1H), 7.67 (t,8Hz,1H), 7.85 (d,8Hz,1H). FAB-MS: calculated for $C_{28}H_{30}N_4O_4$ 486; found 487 (M+H,90%).

Example 96

2-Amino-4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl]-1,1'-biphenyl, trifluoroacetate

A solution of 200mg (0.34mmol) of the intermediate obtained in Example 95 (Step C) in 3mL of methanol was hydrogenated at room temperature and 40psi over 50mg of 5% palladium on carbon for 90 minutes. The catalyst was removed by filtration through Celite and the filtrate evaporated to dryness under vacuum to afford 189mg (0.34mmol,100%) of product.

The above intermediate (90g, 0.16mmol) was dissolved in 5mL of methylene chloride and treated with 0.25mL of trifluoroacetic acid. The mixture was stirred at room temperature for 14 hours then all volatiles removed under vacuum to give 46mg (0.10mmol, 62%) of the title compound. ^{1}H NMR (400MHz,CD_3OD): 1.38 (s,3H), 1.42 (s,3H), 2.13 (m,1H), 2.32 (m,1H), 2.45-2.70 (m,4H), 4.40 (dd;7,11Hz;1H), 5.00 (d,15Hz,1H), 5.29 (d,15Hz,1H), 7.05-7.45 (m,12H). FAB-MS: calculated for $C_{28}H_{32}N_4O_2$ 456; found 457 (M+H,100%).

Example 97

4′-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1′-biphenyl]-2-carboxylic acid-N(2)-formylhydrazide, trifluoroacetate

Step A: 4′-[[3(R)-[(3-t-Butoxycarbonylamino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1′-biphenyl]-2-carboxylic acid-N(2)-formylhydrazide

A solution of 100mg (0.17mmol) of 4′-[[3(R)-[(3-t-butoxycarbonylamino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-thioamide (Example 93, Step A) in 6mL of tetrahydrofuran was treated with 0.08mL of methyl iodide and the resulting solution stirred at room temperature for 14 hours. The mixture was evaporated under vacuum to give the product which was used in the next step without purification.

A solution of 40mg (0.68mmol) of formic hydrazide in 2mL of dry dimethylformamide was added to the intermediate obtained above and the resulting solution stirred at room temperature for 14 hours. An additional 80mg (1.4mmol) of formic hydrazide was added and stirring continued for another 5 hours. The reaction mixture was added to ethyl acetate and washed with water (4x). The organic layer was separated, dried over magnesium sulfate, filtered and solvents removed under vacuum. Purification by preparative thin layer chromatography on silica, eluting with methylene chloride/methanol (9:1), afforded 32mg (0.05mmol, 30%) of product. ^{1}H NMR (200MHz,$CDCl_3$): 1.30 (s,6H), 1.37 (s,9H), 1.84 (m,1H), 2.3-2.6 (m,5H), 4.50 (m,1H), 4.76 (d,15Hz,1H), 4.98 (br s,2H), 5.24 (d,15Hz,1H), 5.53 (br s,1H), 7.1-7.6 (m,12H), 8.34 (br s,1H).

Step B: 4′-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1′-biphenyl]-2-carboxylic acid-N(2)-formyl hydrazide, trifluoroacetate

Prepared from the intermediate obtained in Step A by the procedure described in Example 69, Step F.^{1}H NMR (400MHz,CD_3OD): 1.35 (s,3H), 1.39 (s,3H), 2.12 (m,1H), 2.22 (m,1H), 2.35-2.70 (m,4H), 4.39 (m,1H), 4.9 (m,1H), 5.3 (m,1H), 7.2-7.8 (m,12H), 8.20 (s,1H). FAB-MS: calculated for $C_{30}H_{33}N_5O_4$ 527; found 534 (M+Li,10%).

Example 98

4′-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-(hydroxyacetyl)-1,1′-biphenyl, trifluoroacetate

Step A: 4′-Methyl-2-acetyl-1,1′-biphenyl

Prepared from 4-methylphenyltrimethylstannane (Example 69, Step A) and 2′-bromoacetophenone by the procedure described in Example 69, Step B. ^{1}H NMR (200MHz,$CDCl_3$): 1.98 (s,3H), 2.37 (s,3H), 7.20 (s,4H), 7.3-7.5 (m,4H). FAB-MS: calculated for $C_{15}H_{14}O$ 210; found 211 (M+H,100%).

Step B: 4′-Methyl-2-(bromoacetyl)-1,1′-biphenyl

A solution of 4′-methyl-2-acetyl-1,1′-biphenyl (2.06g,9.79mmol) in 10mL of glacial acetic acid was treated dropwise with a solution of bromine (1.722g,1.07mmol) dissolved in 3.0mL of glacial acetic acid. After initiating the reaction with the first few drops of the bromine/acetic acid reagent by heating the reaction mixture at 30°C, the remainder of the bromine solution was added dropwise at 25-30 °C. The reaction mixture was stirred at room temperature until the consumption of bromine was complete (approximately 2 hrs). The reaction mixture was diluted with 150mL of hexane then washed with water (3x50mL). The organic layer was removed, dried over magnesium sulfate, filtered and evaporated under vacuum to give 2.92g of an oil that was used in the next step without purification. ^{1}H NMR (crude product) (200MHz,$CDCl_3$): 2.38 (s,3H), 3.66 (s,2H), 7.21 (s,4H), 7.3-7.6 (m,4H).

Step C: 4′-Methyl-2-(acetoxyacetyl)-1,1′-biphenyl

A solution of 1.44g (4.98mmol) of 4′-methyl-2-(bromoacetyl)-1,1′-biphenyl in 3.0mL of polyethyleneglycol-400 was added to a solution of 500mg of potassium acetate in 3.0mL of polyethyleneglycol-400. The suspension was heated at 100°C for 30 minutes, then cooled and diluted with 100mL of water. The resultant mixture

was extracted with ether; the combined ether extracts were diluted with an equal volume of hexane and washed with water. The organic layer was separated, dried over magnesium sulfate, filtered, and the solvent was removed under vacuum to yield an oil which was purified by silica chromatography, eluting with hexane/ethyl acetate (8:1) to give 444mg (1.66mmol,33%) of product as an oil. ^{1}H NMR (200MHz, $CDCl_3$): 2.06 (s,3H),

Step D: 4'-Bromomethyl-2-(acetoxyacetyl)-1,1'-biphenyl

Prepared from 4'-methyl-2-(acetoxyacetyl)-1,1'-biphenyl by the procedure described in Example 69, Step C. ^{1}H NMR (200MHz), $CDCl_3$): 2.01 (s,3H), 4.49 (s,4H), 7.15-7.55 (m,8H).

Step E: 3-[[1-[[2'-(acetoxyacetyl)-[1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepin-3(R)-yl]amino]-1,1-dimethyl-3-oxopropylcarbamic acid, 1,1-dimethylethyl ester

Prepared from 4'-bromomethyl-2-(acetoxy-acetyl)-1,1'-biphenyl and 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) by the procedure described in Example 69, Step D. ^{1}H NMR (200MHz, $CDCl_3$): 1.33 (s,6H), 1.39 (s,9H), 1.87 (m,1H), 2.03 (s,3H), 2.35-2.70 (m,5H), 4.36 (s,2H), 4.51 (m,1H), 4.85 (d,15Hz,1H), 5.28 (d,15Hz,1H), 6.66 (m,1H), 7.1-7.6 (m, 12H).

Step F: 4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-(hydroxyacetyl)-1,1'-biphenyl, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step E by the procedure described in Example 69, Step F. ^{1}H NMR (200MHz,CD_3OD): 1.30 (s,3H), 1.34 (s,3H), 2.08 (m,1H), 2.28 (m,1H), 2.4-2.6 (m,4H), 4.01 (s,2H), 4.36 (dd;8,11Hz;1H), 4.95 (d,15Hz,1H), 5.17 (d,15Hz,1H), 7.1-7.5 (m,12H). FAB-MS (Li^+ spike): calculated for $C_{30}H_{33}N_3O_4$ 499; found 500 (M+H,18%), 506 (M+Li,100%).

Example 99

4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl]-2-hydroxy-1,1'-biphenyl, trifluoroacetate

Step A: 4'-Methyl-2-hydroxy-1,1'-biphenyl

A solution of 4.2g (20.0mmol) of 4'-methyl-2-acetyl-1-1'-biphenyl (Example 98, Step A) in methylene chloride, under a nitrogen atmosphere, was treated with 8.98g of 85% m-chloroperbenzoic acid. The resultant suspension was cooled to 0°C and treated dropwise with 1.54mL of trifluoroacetic acid over a 10 minute period. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with 50mL of methylene chloride and the solution was washed successively with 50mL of 10% sodium sulfite, 50mL of saturated aqueous potassium carbonate and water (3x50mL). The organic layer was removed and dried over magnesium sulfate, then evaporated under vacuum to yield 4.1g of an oil. The oil was dissolved in 20mL of methanol and treated with 2.0mL of 5N aqueous sodium hydroxide. The reaction mixture was stirred at room temperature for 1 hour. The pH of the solution was adjusted to 5-6 with acetic acid. After the methanol was removed under vacuum, the residue was taken up in ether, washed with water, dried over magnesium sulfate, filtered and evaporated under vacuum to yield 3.0g of crude product which was purified by preparative high pressure liquid chromatography on silica, eluting with hexane/ethyl acetate (10:1). In this manner, 1.85g (10.0mmol,50%) of the product was obtained as an oil. ^{1}H NMR (200MHz, $CDCl_3$): 2.40 (s,3H), 5.22 (br s,1H), 6.96 (m,2H), 7.2-7.4 (m,6H). EI-MS: calculated for $C_{13}H_{12}O$ 184; found 184 (M^+,100%).

Step B: 4'-Methyl-2-acetoxy-1,1'-biphenyl

A solution of 1.0g (5.4mmol) of 4'-methyl-2-hydroxy-1,1'-biphenyl in 2.0mL of pyridine was treated with 2mL of acetic anhydride. The reaction mixture was stirred at room temperature for 5 hours The solvent was removed under vacuum to yield 1.11g (4.9mmol,90 %) of the product as an oil. ^{1}H NMR (200MHz,$CDCl_3$): 2.07 (s,3H), 2.36 (s,3H), 7.07 (dd;3,8Hz;1H), 7.15 (d,8Hz,2H), 7.2-7.4 (m,5H).

Step C: 4'-Bromomethyl-2-acetoxy-1,1'-biphenyl

Prepared from 4'-methyl-2-acetoxy-1,1'-biphenyl by the procedure described in Example 69, Step C. ^{1}H

NMR (200MHz,$CDCl_3$): 2.05 (s,3H), 4.50 (s,2H), 7.08 (m,1H), 7.20-7.45 (m,7H).

Step D: 3-[[1-[[2'-acetoxy-[1,1'-biphenyl]-4-yl]-methyl]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepin-3(R)-yl]amino]-1,1-dimethyl-3-oxopropylcarbamic acid, 1,1-dimethylethyl ester

Prepared from 4'-bromomethyl-2-acetoxy-1,1'-biphenyl and 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) by the procedure described in Example 69, Step D. ^{1}H NMR (200MHz, $CDCl_3$): 1.38 (s,6H), 1.45 (s,9H), 1.85 (m,1H), 2.02 (s,3H), 2.35-2.65 (m,5H), 4.52 (m,1H), 4.84 (d,15Hz,1H), 5.30 (d,15Hz,1H), 6.71 (d,7Hz,1H), 7.1-7.4 (m,12H).

Step E: 4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-hydroxy-1,1'-biphenyl, trifluoroacetate

A solution of 468mg (0.78mmol) of the intermediate obtained in Step D in 25mL of methanol was treated with 4.0mL of 5N aqueous sodium hydroxide and the resultant solution stirred at room temperature for 1 hour. The solvent was removed under vacuum to yield the crude intermediate which was used without purification.

The intermediate obtained above was treated as described in Example 69, Step F to afford the title compound. ^{1}H NMR (400MHz,CD_3OD): 1.34 (s,3H), 1.39 (s,3H), 2.11 (m,1H), 2.32 (m,1H), 2.45-2.70 (m,4H), 4.41 (dd;8,11Hz;1H), 4.95 (d,15Hz,1H), 5.23 (d,15Hz,1H), 6.86 (d,8Hz,2H), 7.11 (m,1H), 7.15-7.25 (m,5H), 7.35 (m,2H), 7.45 (d,8Hz,2H).

Example 100

4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]- methyl]-2-(4-aminophenoxy)-1,1'-biphenyl di(trifluoroacetate)

Step A: 4'-Methyl-2-(4-nitrophenoxy)-1,1'-biphenyl

A solution of 450mg (2.44mmol) of 4'-methyl-2-hydroxy-1-1'-biphenyl (Example 99, Step A) in 7.0mL of dimethylformamide was treated with 135mg of 60% sodium hydride (3.3mmol). The reaction mixture was stirred at room temperature for 30 minutes then treated with 428mg (3.03mmol) of 1-fluoro-2-nitro-benzene. The reaction mixture was htated at 100°C for 2 hours. The reaction mixture was cooled, poured into 100mL of water and the resultant mixture was extracted with ethyl ether (3x60mL). The combined extracts were washed with water (4x50mL), dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was chromatographed on silica, eluting with hexane/ethyl acetate (10:1) to give 737mg (99%) of the product. ^{1}H NMR (200MHz,$CDCl_3$): 2.28 (s,3H), 6.83 (d,8Hz,2H), 7.08 (d,8Hz,2H), 7.3-7.5 (m,6H), 8.05 (d,8Hz,2H).

Step B: 4'-Bromomethyl-2-(4-nitrophenoxy)-1,1'-biphenyl

Prepared from 4'-methyl-2-(4-nitrophenoxy)-1,1'-biphenyl by the procedure described in Example 69, Step C. ^{1}H NMR (200MHz,$CDCl_3$): 4.43 (s,2H), 6.83 (d,8Hz,2H), 7.09 (d,8Hz,1H), 7.3-7.5 (m,7H), 8.04 (d,8Hz,2H).

Step C: 3-[[1-[[2'-(4-nitrophenoxy)-[1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepin-3(R)-yl]amino]-1,1-dimethyl-3-oxopropylcarbamic acid, 1,1-dimethylethyl ester

Prepared from 4'-bromomethyl-2-(4-nitro-phenoxy)-1,1'-biphenyl and 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) by the procedure described in Example 69, Step D.^{1}H NMR (200MHz,$CDCl_3$): 1.32 (s,6H), 1.38 (s,9H), 1.78 (m,1H), 2.3-2.7 (m,5H), 4.47 (m,1H), 4.75 (d,15Hz, 1H), 5.13 (d,15Hz,1H), 6.63 (d,7Hz,1H), 6.75 (d,8Hz,2H), 7.05-7.50 (m,/11H), 7.97 (s,1H), 7.98 (d,8Hz,2H).

Step D: 4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-(4-aminophenoxy)-1,1'-biphenyl, di(trifluoroacetate)

The intermediate obtained in Step C (140mg,0.21mmol) was dissolved in 16mL of methanol and hydrogenated at room temperature and 40psi over 20mg of 10% palladium on carbon for 2 hours. The catalyst was removed by filtration through Celite and the filtrate evaporated under vacuum to yield 140mg of crude product which was used in the next step without purification.

The crude intermediate obtained above was converted to the title compound by treatment with trifluoroacetic acid according to the procedure described in Example 69, Step F. ^{1}H NMR (200MHz, CD_3OD): 1.38 (s,3H), 1.42 (s,3H), 2.11 (m,1H), 2.32 (m,1H), 2.45-2.65 (m,4H), 4.41 (dd;8,12Hz;1H), 4.88 (d,15Hz,1H), 5.25 (d,15Hz,1H), 6.90 (d,8Hz,2H), 7.09 (d,8Hz,1H), 7.15-7.50 (m,13H).

Examplee 101

3-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]phenyl-acetamide, trifluoroacetate

Step A: 3-(Bromomethyl)phenylacetonitrile

Prepared from 3-(methyl)phenylacetonitrile by the procedure described in Example 69, Step C. ^{1}H NMR (300MHz,$CDCl_3$): 3.73 (s,2H), 4.45 (s,2H), 7.24 (m,1H), 7.33 (m,3H).

Step B: 3-[[1-[[1-(Cyanomethyl)phenyl-3-yl]methyl]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepin-3(R)-yl]amino]-1,1-dimethyl-3-oxopropylcarbamic acid 1,1-dimethylethyl ester

Prepared from 3-(bromomethyl)phenylacetonitrile and 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) by the procedure described in Example 69, Step D. ^{1}H NMR (400MHz,$CDCl_3$): 1.33 (s,3H), 1.34 (s,3H), 1.40 (s,9H), 1.83 (m,1H), 2.4-2.6 (m,5H), 3.65 (s,2H), 4.48 (m,1H), 4.86 (d,15Hz,1H), 5.12 (d,15Hz,1H), 5.23 (br s,1H), 6.60 (d,7Hz,1H), 7.1-7.3 (m,8H). FAB-MS: calculated for $C_{29}H_{36}N_4O_4$ 504; found 505 (M+H,10%).

Step C: 3-[[3(R)-[(3-t-Butoxycarbonylamino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]phenylacetamide

Prepared from the intermediate obtained in Step B by the procedure described in Example 69, Step E. ^{1}H NMR (400MHz,$CDCl_3$): 1.32 (s,6H), 1.39 (s,9H), 1.90 (m,1H), 2.4-2.6 (m,5H), 3.46 (d,15Hz,1H), 3.50 (d,15Hz,1H), 4.48 (m,1H), 4.93 (d,15Hz,1H), 5.07 (d,15Hz,1H), 5.49 (br s,1H), 5.93 (br s,1H), 6.65 (d,7Hz,1H), 7.05-7.25 (m,8H). FAB-MS: calculated for $C_{29}H_{38}N_4O_4$ 506; found 507 (M+H,15%).

Step D: 3-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]phenylacetamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 69, Step F. ^{1}H NMR (200MHz, CD_3OD): 1.30 (s,3H), 1.33 (s,3H), 2.07 (m,1H), 2.26 (m,1H), 2.4-2.6 (m,4H), 3.39 (s,2H), 4.33 (dd;8,11Hz;1H), 4.90 (d,15Hz,1H), 5.11 (d,15Hz,1H), 7.08 (d,8Hz,1H), 7.1-7.2 (m,5H), 7.25 (d,2Hz,2H). FAB-MS: calculated for $C_{23}H_{28}N_4O_3$ 422; found 423 (M+H,100%).

Example 102

3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-etrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 3-[(2-(R)-Benzyloxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

Prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 1) and (R)-2-benzyloxlpropanal (prepared from ethyl-D-lactate according to the procedure of Hanessian and Kloss, Tetrahedron Lett. **1985**, 26, 1261-1264.) by the procedure described in Example 86, Step A. ^{1}H NMR (200MHz,CD_3OD): 1.25 (d,6Hz,3H), 1.35 (s,6H), 2.11 (m,1H), 2.32 (m,1H), 2.5-2.7 (m,4H), 2.95 (m,1H), 3.17 (m,1H), 3.80 (m,1H), 4.40 (m,1H), 4.44 (d,11Hz,1H), 4.64 (d,11Hz,1H), 4.90 (d,15Hz,1H), 5.02 (d,15Hz,1H), 6.99 (d,8Hz,2H), 7.1-7.7 (m,15H). FAB-MS: calculated for $C_{39}H_{43}N_7O_3$ 657; found 658 (M+H,100%).

Step B: 3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 86, Step B. ^{1}H NMR (400MHz,CD_3OD): 1.22 (d,6Hz,3H), 1.37 (s,3H), 1.39 (s,3H), 2.10 (m,1H), 2.31 (m,1H), 2.45-2.70 (m,4H), 2.81 (dd;10,12Hz;1H), 3.08 (dd;4,12Hz;1H), 3.92 (m,1H), 4.36 (dd;7,11Hz;1H), 4.93 (d,15Hz,1H), 5.17 (d,15Hz,1H), 7.04 (d,8Hz,2H), 7.19 (d,8Hz,2H), 7.20-7.35 (m,4H), 7.54 (m,2H), 7.65 (m,2H). FAB-MS: calculated for $C_{32}H_{37}N_7O_3$ 567; found 568 (M+H,45%).

Example 103

2-[(2(R)-Hydroxypropyl)amino]-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, trifluoroacetate

The title compound was prepared from 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, trifluoroacetate (Example 63) and (R)-2-benzyloxypropanal (prepared from ethyl-D-lactate according to the procedure of Hanessian and Kloss, Tetrahedron Lett. **1985**, 26, 1261-1264.) by the procedures described in Example 86. ^{1}H NMR (200MHz,CD_3OD): 1.16 (d,6Hz,3H), 1.55 (s,3H), 1.64 (s,3H), 2.22 (m,2H), 2.49 (m,2H), 2.74 (dd;9,12Hz; 1H), 2.92 (dd;4,12Hz;1H), 3.94 (m,1H), 4.31 (m,1H), 4.88 (d,15Hz,1H), 5.17 (d,15Hz,1H), 6.98 (d,8Hz,2H), 7.16 (d,8Hz,2H), 7.2-7.4 (m,4H), 7.45-7.70 (m,4H). FAB-MS: calculated for $C_{31}H_{35}N_7O_3$ 553; found 554 (M+H,45%).

Example 104

3-[(2(R)-Acetoxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

To a stirred solution of 20mg (0.028mmol) of 3-[(2(R)-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 102) in 2mL of methylene chloride at room temperature was added 8.8mg of acetic anhydride (3eq.) followed by 13mg (4eq.) of 4-dimethylaminopyridine. The mixture was stirred for one hour then concentrated under vacuum and the residue purified by reverse phase high pressure liquid chromatography on C18, eluting with methanol/ 0.1%aqueous trifluoroacetic acid (70:30) to afford the title compound.
^{1}H NMR (400MHz, CD_3OD): 1.30 (d,6Hz,3H), 1.36 (s,3H), 1.39 (s,3H), 2.01 (s,3H), 2.10 (m,1H), 2.29 (m,1H), 2.4-2.7 (m,4H), 3.15 (dd;9,13Hz,1H), 3.25 (dd;4,13Hz,1H), 4.36 (dd;8,12Hz,1H), 4.9 (d,15Hz,1H), 5.07 (m,1H), 5.19 (d,15Hz,1H), 7.04 (d,8Hz,2H), 7.19 (d,8Hz,2H), 7.20-7.35 (m,4H), 7.54 (m,2H), 7.65 (m,2H). FAB-MS: calculated for $C_{34}H_{39}N_7O_4$ 609; found 610 (M+H,75%).

Example 105

3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1-methyltetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 3-[(2-(R)-Benzyloxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1-methyltetrazol-5-yl)[1,1′-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

Prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1-methyltetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 16) by the procedure described in Example 86, Step A. ^{1}H NMR (200MHz,CD_3OD): 1.29 (d,7Hz,3H), 1.35 (s,6H), 2.12 (m,1H), 2.35 (m,1H), 2.5-2.7 (m,4H), 3.00 (dd;9,13Hz;1H), 3.14 (s,3H), 3.20 (m,1H), 3.85 (m,1H), 4.44 (m,1H), 4.48 (d,11Hz,1H), 4.67 (d,11Hz,1H), 4.90 (d,15Hz,1H), 5.25 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.1-7.5 (m,12H), 7.6 (m,2H), 7.75 (m,1H). FAB-MS: calculated for $C_{40}H_{45}N_7O_3$ 671; found 672 (M+H,100%).

Step B: 3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2-(1-methyl-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 86, Step B. ^{1}H NMR (200MHz,CD_3OD): 1.21 (d,6Hz,3H), 1.34 (s,3H), 1.36 (s,3H), 2.10 (m,1H), 2.20-

2.70 (m,5H), 2.78 (dd;10,12Hz;1H), 3.09 (dd;4,12Hz;1H), 3.16 (s,3H), 3.92 (m,1H), 4.35 (dd;8,12Hz;1H), 4.85 (d,15Hz,1H), 5.32 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.15-7.35 (m,6H), 7.55-7.75 (m,4H). FAB-MS: calculated for $C_{33}H_{39}N_7O_3$ 581; found 582 (M+H,100%).

Example 106

3-[(2(R)-Methoxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 2(R)-Methoxypropionaldehyde

To a solution of 1.00g (9.6mmol) of (R)-(+)-methyl lactate in 2 mL of methyl iodide was added 4.45g (19.2mmol) of silver (I) oxide and the resulting mixture heated at reflux for 2 hours. The mixture was cooled, filtered and the excess methyl iodide removed under vacuum at 0°C to afford 0.5g of crude methyl [2(R)-methoxy]propionate which was used in the next step without purification.

To a stirred solution of 0.5g (4.2mmol) of the intermediate obtained above in 5mL of ether at 0°C was added 5.0mL of 1.0M solution of lithium aluminum hydride in ether over 5 minutes. The resulting mixture was treated with 1mL of 1N sodium hydroxide, filtered, dried over magnesium sulfate and concentrated under vacuum at 0°C to give 0.36g of crude 2(R)-methoxypropanol which was used directly in the next step.

To a stirred suspension of 2.7g (12.6mmol) of pyridinium chlorochromate on Celite (1g) in 8mL of methylene chloride was added 0.36g of crude 2(R)-methoxypropanol and the resulting mixture stirred at room temperature for 3 hours. The reaction mixture was filtered, dried over sodium sulfate, filtered and concentrated under vacuum at 0°C to give approximately 0.3g of crude product which was used in the next step without purification.

Step B: 3-[(2(R)-Methoxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 1) and 2(R)-methoxypropionaldehyde (Step A) by the procedure described in Example 86, Step A. ^{1}H NMR (200MHz,CD_3OD): 1.17 (d,6Hz,3H), 1.36 (br s,6H), 2.11 (m,1H), 2.31 (m,1H), 2.45-2.65 (m,4H), 2.87 (m,1H), 3.14 (m,1H), 3.31 (s,3H), 3.59 (m,1H), 4.37 (dd;7,11Hz;1H), 4.95 (d,15Hz,1H), 5.15 (d,15Hz,1H), 7.03 (d,8Hz,2H), 7.1-7.4 (m,6H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{33}H_{39}N_7O_3$ 581; found 582 (M+H,100%).

Example 107

3-[(2-Hydroxy-2-methylpropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 2-Benzyloxy-2-methyl-3-butene

To a stirred suspension of 18.6g of 60% sodium hydride oil dispersion (0.46mol) in 50mL of dry tetrahydrofuran at 0°C was added 40g (0.46mol) of 2-methyl-3-buten-2-ol over 30 minutes. The resulting mixture was warmed to room temperature and stirred for 3 hours, then heated at reflux for an additional 30 minutes. The mixture was cooled to 0°C, treated with 80g (0.46mol) of benzyl bromide, then heated at reflux for 5 hours. The reaction mixture was cooled, filtered and concentrated under vacuum. The residue was purified by distillation under reduced pressure to give 42g (0.24mol,52%) of product, b.p. 88-89°C (2mm). ^{1}H NMR (200MHz, $CDCl_3$): 1.38 (s,6H), 4.39 (s,2H), 5.20 (m,2H), 5.95 (m,1H), 7.27-7.4 (m,5H).

Step B: 2-Benzyloxy-2-methylpropionaldehyde

A mixture of 100mL of water, 300mL of dioxane, 20g (0.11mol) of 2-benzyloxy-2-methyl-3-butene and 1g of osmium tetroxide was stirred at room temperature for 30 minutes then 51g (0.22mol) of finely ground sodium periodate was added in portions over 30 minutes. Stirring was continued for 2 hours then the mixture filtered and the filtrate extracted with several portions of ether. The combined extracts were dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. Distillation afforded 7.3g (0.041mol,37%) of product, b.p. 85-88°C (2mm).

Step C: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

To a solution of 150mg (0.40mmol) of 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) in 2mL of methylene chloride at 0°C was added 2mL of trifluoroacetic acid and the mixture stirred at room temperature for 1 hour. All volatiles were removed under vacuum to give 130mg (0.33mmol,84%) of the product.
^{1}H NMR (200MHz, CD_3OD): 1.33 (s,3h), 1.37 (s,3H), 2.12 (M,1H), 2.3-2.6 (m,3H), 2.6-3.0 (m,2H), 4.37 (dd;8,12Hz;1H), 7.02 (d,8Hz,1H), 7.1-7.3 (m,3H). FAB-MS: calculated for $C_{15}H_{21}N_3O_2$ 275; found 276 (M+H,100%).

Step D: 3-(2-Benzyloxy-2-methylpropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-(R)-yl]-butanamide

Prepared from the intermediate obtained in Step C and 2-benzyloxy-2-methylpropionaldehyde by the procedure described in Example 86, Step A.
^{1}H NMR (200MHz, CD_3OD): 1.32 (s,3H), 1.38 (s,9H), 2.10 (m,1H), 2.41 (m,1H), 2.65 (s,2H), 2.7-2.9 (m,2H), 3.09 (s,2H), 4.40 (m,1H), 4.48 (s,2H), 7.0-7.2 (m,4H), 7.2-7.4 (m,5H). FAB-MS: calculated for $C_{26}H_{35}N_3O_3$ 437; found 438 (M+H,100%).

Step E: 3-[(2-Benzyloxy-2-methylpropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

To a stirred solution of 145mg (0.332mmol) of the intermediate obtained in Step D in 2mL of dry dimethylformamide at room temperature under nitrogen was added 67mg of 60% sodium hydride oil dispersion (1.67mmol,5eq.). After 30 minutes, a solution of 277mg (0.41mmol,1.2eq.) of N-triphenylmethyl-5-[2-(4′-bromomethylbiphen-4-yl)] tetrazole in 2mL of dry dimethylformamide was added and the mixture stirred at room temperature for 1 hour. The reaction mixture was added to 100mL of ethyl acetate and washed with water (2x) and brine. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated under vacuum.
The residue was dissolved in 5mL of methanol and treated with 5mL of 9N HCl. The mixture was stirred at room temperature for 2 hours then washed with hexanes (5x) to remove triphenylmethanol. The aqueous layer was removed, filtered and evaporated under vacuum; the residue was purified by reverse phase medium pressure liquid chromatography on C8, eluting with methanol/0.1% aqueous trifluoroacetic acid (65:35) to afford 245mg (0.31mmol,94%) of product.
^{1}h NMR (200MHz,CD_3OD): 1.32 (s,3H), 1.38 (s,9H), 2.10 (m,1H), 2.31 (m,1H), 2.4-2.7 (m,2H), 2.66 (s,H), 4.39 (dd;7,11Hz;1H), 4.50 (s,2H), 4.94 (d,15Hz,1H), 5.16 (d,15Hz,1H), 6.99 (d,8Hz,2H), 7.05-7.25 (m,5H), 7.25-7.45 (m,6H), 7.55-7.70 (m,4H). FAB-MS: calculated for $C_{40}H_{45}N_7O_3$ 671; found 672 (M+H,100%).

Step F: 3-[(2-Hydroxy-2-methylpropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step E by the procedure described in Example 86, Step B.
^{1}H NMR (200MHz,CD_3OD): 1.29 (s,6H), 1.36 (s,3H), 1.40 (s,3H), 2.1-2.5 (m,4H), 2.68 (s,2H), 2.98 (s,2H), 4.37 (dd;7,11Hz;1H), 4.94 (d,15Hz,1H), 5.17 (d,15Hz,1H), 7.04 (d,8Hz,2H), 7.20 (d,8Hz,2H), 7.20-7.35 (m,4H), 7.5-7.7 (M,4H). FAB-MS: calculated for $C_{33}H_{39}N_7O_3$ 581; found 582 (M+H,70%).

Example 108

3-[(2(S)-Hydroxy-3-methylbutyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 3-[(2(S)-Benzyloxy-3-methylbutyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl](methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Prepared from 2(S)-benzyloxy-3-methylbutanal (prepared from L-valine by the method of Li, et al; J. Amer. Chem. Soc., 112, 7659 (1990)) and 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-

yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 1), by the procedure described in Example 86, Step A. ^{1}H NMR (200MHz, CD_3OD): 0.92 (d,7Hz, 3H), 0.98 (d,7Hz, 3H) 1.31 (s,3H), 1.38 (s,3H), 2.0-2.6 (m,5H), 2.62 (s,2H), 2.95 (dd;9,12Hz;1H), 4.89 (d,15Hz,1H), 5.18 (d,15Hz,1H), 6.97 (d,8Hz,2H), 7.1-7.7 (m,15H). FAB-MS: calculated for $C_{41}H_{47}N_7O_3$ 685, found 687 (100%).

Step B: 3-[(2(S)-Hydroxy-3-methylbutyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Prepared from the intermediate obtained in Step A by the procedure described in Example 86, Step B. ^{1}H NMR (200MHz, CD_3OD): 0.86 (d,7Hz,3H), 0.92 (d,7Hz,3H), 1.35 (s,3H), 1.40 (s,3H), 1.67 (m,1H), 2.0-2.6 (m,4H), 2.64 (s,2H), 2.82 (dd;10,12Hz,1H), 3.12 (dd;3,12Hz;1H), 3.48 (m,1H), 4.37 (dd;8,12Hz,1H), 4.9 (d,15Hz,1H), 5.19 (d,15Hz,1H), 7.04 (d,8Hz,2H), 7.15-7.35 (m,6H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{34}H_{41}N_7O_3$ 595; found 597 (100%).

Example 109

3-[(2(R)-Hydroxy-3-methylbutyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from D-valine and 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-([2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 1), by the procedures described in Example 108.
^{1}H NMR (200MHz, CD_3OD): 0.86 (d,7Hz,3H), 0.88 (d,7Hz,3H), 1.32 (s,3H), 1.33 (s,3H), 1.65 (m,1H), 2.00-2.66 (m,6H), 2.78 (dd;10,12Hz,1H), 3.10 (dd;2,12Hz,1H), 3.45 (m,1H), 4.34 (dd;8,12Hz,1H), 4.90 (d,15Hz,1H), 5.1 (d,15Hz,1H), 7.02 (d,8Hz,2H), 7.1-7.3 (m,6H), 7.45-7.70 (m,4H). FAB-MS: calculated for $C_{34}H_{41}N_7O_3$ 595; found 597 (100%).

Example 110

4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-phenyl-1,1'-biphenyl, trifluoroacetate

Step A : 2-Bromobiphenyl

A solurion of 8.8mL of isoamylnitrite in 120mL of benzene ar 45°C was treated dropwise over 30 minutes with a solution of 7.5g of 2-bromoaniline in 30mL of benzene. After the addition was complete, the mixture was heated at reflux for 90 minutes then cooled and concentrated under vacuum. The product was purified by preparative high presssure liquid chromatography on silica, eluting with hexanes. ^{1}H NMR (200MHz,$CDCl_3$): 7.23 (m,2H), 7.35 (m,1H), 7.44 (s,5H), 7.70 (d,8Hz,1H).

Step B: 4'-Methyl-2-phenyl-1,1'-biphenyl

Prepared from 2-bromobiphenyl and 4-methylphenyltrimethylstannane by the procedure described in Example 69, Step B.
^{1}H NMR (200MHz,$CDCl_3$): 2.30 (s,3H), 7.06 (s,4H), 7.23 (m,5H), 7.44 (s,4H).

Step C: 4'-Bromomethyl-2-phenyl-1,1'-biphenyl

Prepared from 4'-methyl-2-phenyl-1,1'-biphenyl by the procedure described in Example 69, Step C.

Step D: 4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-phenyl-1,1'-biphenyl, trifluoroacetate

The title compound was prepared from 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) and 4'-bromomethyl-2-phenyl-1,1'-biphenyl by the procedures described in Example 69,.Steps D and F. ^{1}H NMR (300MHz,CD_3OD): 1.32 (s,3H), 1.36 (s,3H) 2.0-2.6 (m,6H), 4.37 (dd;8,12Hz;1H), 4.78 (d,15Hz,1H), 5.28 (d,15Hz,1H), 6.95-7.45 (m,17H).

Example 111

3-[[2-Hydroxy-3-(4-hydroxyphenyl)-propyl]amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: Ethyl 2-hydroxy-3-(4-hydroxyphenyl)-propionate

To a stirred solution of 0.5g (2.74mmol) of D,L 3-(4-hydroxyphenyl) lactic acid hydrate in 10mL of ethanol was added a catalytic amount of concentrated hydrochloric acid. The mixture was heated at reflux for 2 hours then cooled to room temperature and concentrated under vacuum. The residue was dissolved in 50mL of ether and washed with saturated aqueous sodium bicarbonate (1x50mL) and brine (1x50mL). The organic layer was removed, dried over magnesium sulfate, filtered and evaporated under vacuum to afford 0.54g (2.57mmol,94%) of the ethyl ester. ^{1}H NMR (200MHz,$CDCl_3$): 1.26 (t,7Hz,3H), 2.86 (dd;7,14Hz;1H), 3.03 (dd;4,1HZ;1H), 4.19 (q,7Hz,2H), 4.38 (dd;4,7Hz,1H), 5.60 (br s,1H), 6.66 (d,8Hz,2H), 7.03 (d,8Hz,2H).

Step B: Ethyl 2-(t-butyldimethylsiloxy)-3-[4-(t-butyldimethylsiloxyphenyl)]propionate

To a stirred solution of 0.57g (7.4mmol) of ethyl 2-hydroxy-3-(4-hydroxyphenyl)propionate in 10mL of methylene chloride at -78°C was added 2mL of 2,6-lutidine (4eq.) followed by 2.52mL of t-butyldimethylsilyl trifluoromethanesulfonate (4eq.). The reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was diluted with 50mL of methylene chloride and washed with 10% hydrochloric acid (2x100mL), saturated aqueous sodium bicarbonate and brine. The organic layer was removed, dried over magnesium sulfate, filtered and concentrated under vacuum to give 1.12g of crude product. A 250mg sample was purified by preparative thin layer chromatography on silica, eluting with hexane/ethyl acetate (90:10) to afford 210mg of pure product. ^{1}H NMR (200MHz,$CDCl_3$): 0.13 (s,6H), 0.76 (s,9H), 0.94 (s,9H), 2.76 (dd;10,14Hz,1H), 2.97 (dd;4,14Hz;1H), 4.24 (dd;4,10Hz,1H), 6.73 (d,8Hz,2H), 7.05 (d,8Hz,2H).

Step C: 2-(t-Butyldimethylsiloxy)-3-[4-(t-butyl-dimethylsiloxyphenyl)]propanal

To a stirred solution of 210mg (0.48mmol) of ethyl 2-(t-butyldimethylsiloxy)-3-[4-(t-butyldimethylsiloxyphenyl)]propionate in 10mL of ether at -78°C was added dropwise over 5 minutes 1mL of 1.0M solution of diisobutylaluminium hydride in hexane (2eq.). The reaction mixture was poured, with rapid stirring, into 50mL of 10% hydrochloric acid. After stirring for 5 minutes, the mixture was extracted with ether (2x30mL) and the combined extracts dried over magnesium sulfate, filtered and concentrated under vacuum to give approximately 200mg of the product which was used immediately and without further purification.
^{1}H NMR (200MHz,$CDCl_3$): 0.14 (s,6H), 0.80 (s,9H), 0.95 (s,9H), 2.76 (dd;10,14Hz;1H), 2.90 (dd;4,14Hz;1H), 4.24 (ddd;2,4,10Hz;1H), 6.73 (d,8Hz,2H), 7.02 (d,8Hz,2H), 9.61 (d,2Hz,1H).

Step D: 3-[(2-Hydroxy-3-(4-hydroxyphenyl)-propyl)-amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared as a mixture of two diastereomers from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide,trifluoroacetate (Example 1) and 2-(t-butyldimethylsiloxy)-3-[4-(t-butyldimethylsiloxyphenyl)]propanal (Step C) by the procedure described in Example 86, Step A.
^{1}H NMR (200MHz, CD_3OD): 1.35 (m,6H), 2.10 (m,1H), 2.29 (m,1H), 2.40-2.75 (m,6H), 2.85 (m,1H), 3.07 (m,1H), 3.90 (m,1H), 4.33 (dd;8,12Hz;1H), 4.9 (m,1H), 5.1 (m,1H), 6.67 (d,8Hz,2H), 7.02 (m,4H), 7.15-7.35 (m,6H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{38}H_{41}N_7O_4$ 659; found 659 (40%).

Example 112

3-[[2(R)-Hydroxy-2-phenylpropyl]amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 2(R)-Benzyloxy-2-phenylacetaldehyde

Prepared from (R)-(-)-mandelic acid by the procedures described in Example 111 (Steps A, C) and Example 107, Step A.

^{1}H NMR (200MHz,$CDCl_3$): 4.51 (d,12Hz,1H), 4.65 (d,12Hz,1H), 4.77 (d,2Hz,1H), 7.35 (m,10H), 9.61 (d,2Hz,1H).

Step B: 3-[(2(R)-Benzyloxy-2-phenylethyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl)-butanamide, trifluoroacetate

Prepared 2(R)-benzyloxy-2-phenyl acetaldehyde and 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 1) by the procedure described in Example 86, Step A. ^{1}H NMR (200MHz,CD_3OD): 1.35 (s,6H), 2.12 (m,1H), 2.32 (m,1H), 2.5-2.7 (m,4H), 3.22 (m,2H), 4.32 (d,12Hz,1H), 4.43 (d,12Hz,1H), 4.45 (m,1H), 4.67 (t,7Hz,1H), 4.99 (d,14Hz,1H), 5.13 (d,14Hz,1H), 7.02 (d,8Hz,2H), 7.10-7.45 (m,16H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{44}H_{45}N_7O_3$ 719; found 720 (M+H,35%).

Step C: 3-[[2(R)-Hydroxy-2-phenylpropyl]amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanmide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 86, Step B.
^{1}H NMR (400MHz, CD_3OD): 1.38 (s,3H), 1.39 (s,3H), 2.10 (m,1H), 2.3 (m,1H), 2.4-2.7 (m,4H), 3.05 (m,1H), 3.22 (m,1H), 4.39 (m,1H), 4.95 (d,15Hz,1H), 5.18 (d,15Hz,1H), 7.08 (d,8Hz,2H), 7.20-7.45 (m,11H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{37}H_{39}N_7O_3$ 629; found 630 (M+H,85%).

Example 113

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl)-4-yl]methyl]- 1H-1-benzazepin-3(R)-yl]-butanamide, hydrochloride, dihydrate

Step A: 1-Tetralone oxime

To 4.6L of water at room temperature in a 4-neck 50L flask sitting in a steam bath apparatus equipped with an overhead stirrer, a temperature probe and reflux condenser was added 3.72Kg (27.36mol) of sodium acetate with stirring, followed by 1.9Kg of hydroxylamine hydrochloride (27.36mol). To this slurry at room temperature, 12L of ethanol was added followed by 1.994Kg (13.68mol) of l-tetralone. Additional ethanol (1.7L) was used to rinse off the funnel and added to the reaction mixture. The resulting light orange slurry was heated to 75°C over 40 minutes and maintained at 75-85°C for another 75 minutes. The reaction mixture was cooled with the aid of ice packed around the flask. When the internal temperature reached 32°C, the reaction mixture was pumped over 15 minutes into 60L of ice contained in a 200L vessel. The reaction vessel was washed with an additional 2L of water which was added to the 200L vessel. When the ice melted, the mixture was filtered through a filter pad and the wet cake washed with 4L of water. The wet cake was suction dried for 1 hour then transferred to two trays and dried under vacuum at 40°C for 2 days to give 2.094Kg (13.01mol,95%) of product. ^{1}H NMR (250MHz,$CDCl_3$): 1.90 (m,2H), 2.80 (t,6Hz,2H), 2.88 (t,6Hz,2H), 7.15-7.35 (m,3H), 7.90 (d,8Hz,1H), 8.9 (br s,1H).

Step B: 2,3,4,5-Tetrahydro-1H-1-benzazpin-2-one

To 10L of methanesulfonic acid in a 22L 3-neck flask equipped with an overhead stirrer, a temperature probe, nitrogen inlet and reflux condenser was added 2.6Kg (18.61mol) of phosphorus pentoxide. An additional 1.6L of methanesulfonic acid was used to wash all the phosphorus pentoxide into the vessel. The mixture was heated at 90°C for 2.5 hours then cooled to 50°C using an ice bath and treated with 2.00Kg (12.41mol) of 1-tetralone oxime in several portions over 15 minutes. The mixture was heated at 63°C for 10 minutes then slowly heated to 80°C and kept at 80°C for 3 hours. The reaction mixture was pumped into 70L of ice then treated slowly with 11.25L of 50% aqueous sodium hydroxide over 90 minutes at such a rate so as to maintain the temperature below 28°C. The mixture was filtered and 4L of the filtrate was used to rinse the vessel. The wet cake (pink) was washed with 8L of water then suction dried for 45 minutes then transferred to two trays and dried under vacuum at 40°C for 2 days to give 1.9Kg (11.79mol,95%) of product.^{1}H NMR (250MHz,$CDCl_3$): 2.24 (m,2H), 2.38 (t,6Hz,2H) 2.82 (t,6Hz,2H), 7.03 (d,8Hz,1H), 7.13 (m,1H), 7.24 (m,2H), 8.63 (br s,1H).

Step C: 3-Iodo-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

A suspension of 1.8Kg (11.17mol) of 2,3,4,5-tetrahydro-1H-1-benzazepin-2-one in a mixture of 22.33L of methylene chloride and 11.78L (55.83mol) of hexamethyldisilazane was heated at reflux for 10 minutes then cooled to 30°C and treated with 8.503Kg (33.5mol) of iodine in one portion. The mixture was heated at reflux for 2.5 hours then cooled to room temperature. Aqueous sodium sulfite containing 4.926Kg of sodium sulfite in 44L of water was cooled to 0°C and into it was poured the reaction mixture in several portions with vigorous stirring while maintaining the temperature below 10°C. The reaction vessel was rinsed with 3L of methylene chloride and the washing transferred to the quenching mixture. Methylene chloride (17L) was added to the quenching mixture and it was stirred vigorously and the layers allowed to separate. The aqueous layer was removed and reextracted with 12L of methylene chloride. The combined organic layers were washed with 11L of water and concentrated under vacuum to a final volume of approximately 5L. The residue was treated with 55L of toluene and concentrated under vacuum to a final volume of 10L. The resulting slurry was removed by filtration and the filter cake washed with an additional 5L of toluene and dried under vacuum at ambient temperature for 24 hours to give 1.842Kg (6.42mol,57%) of product.
^{1}H NMR (200MHz,$CDCl_3$): 2.6-2.8 (m,3H), 2.93 (m,1H), 4.64 (t,8Hz,1H), 6.97 (d,8Hz,1H), 7.10-7.35 (m,3H), 7.55 (br s,1H).

Step D: 3(R)-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one, D-tartrate

3-Iodo-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (1.79Kg, 6.24mol) was slurried in 6.2L of methanol and the slurry charged into an autoclave. Condensed ammonia (1.55L) was added and the autoclave closed, with stirring, and heated to 100°C over 1 hour. Heating at 100°C was continued for 2 hours then the autoclave was allowed to cool to room temperature over 1 hour, during which time the internal pressure was 150-155psi. The reaction mixture was transferred to a polyethylene jug and the autoclave rinsed with 2x8L of methanol. The washings were concentrated under vacuum at 30°C then combined with the reaction mixture and concentrated to near dryness under vacuum at 30°C. The resulting residue was dissolved in 4L of ethyl acetate then concentrated to dryness under vacuum at 30°C.

Sodium chloride (712g) was dissolved in 2L of water and 1.0Kg of sodium carbonate was dissolved in 6L of water. Two liters of the sodium carbonate solution was added to the concentrated residue and the resulting slurry transferred to an extraction flask. Another 2L portion of the sodium carbonate solution was added to the residue flask and the solution transferred to the extraction flask. The remaining sodium carbonate solution was used in the same way. The sodium chloride solution was added to the sodium carbonate/aminolactam emulsion and the resulting mixture stirred for 10 minutes then extracted with four 6L portions of methylene chloride. The combined methylene chloride layers were concentrated to dryness; the residue was treated with 2L of 200 proof ethanol and the resulting slurry concentrated to dryness under vacuum to give 1.171Kg of crude product.

The crude product was slurried in 8L of ethanol and treated with 900g of D-tartaric acid in one portion. Water (7L) was added and the mixture heated to 77°C, then additional ethanol (45L) was added and heating continued. The solution was cooled to 43°C and treated with the seed slurry. (The seed slurry was prepared by the route described above starting with 10.50g of crude product and 9.1g of D-tartaric acid.) The solution was aged at room temperature for 48 hours. The slurry formed was removed by filtration and the wet cake washed with 1.8L of ethanol. The resulting filter cake was suction dried with nitrogen bleeding for 20 hours then transferred into a drying tray and dried under vacuum for 24 hours to give 354g (1.085mol, 17.4%) of the product.^{1}H NMR (250MHz,$CDCl_3$): 2.13 (m,1H), 2.51 (m,2H), 2.73 (m,2H), 3.68 (t,6Hz,1H), 3.98 (s,2H), 7.05 (d,8Hz,1H), 7.16 (t,8Hz,1H), 7.30 (m,2H), 7.6 (br s,5H), 10.26 (br s,1H).

Step E: 3(R)-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

A solution of 229.23g (0.700mol) of 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one, D-tartrate in 4.1L of water was treated with 194g (1.40mol) of potassium carbonate. Subsequent portions of 100g and 135g of potassium carbonate were added until the pH was 10.5. The mixture was extracted with four 4L portions of methylene chloride which were then combined and dried over magnesium sulfate. The aqueous layer was treated with 1.4Kg of sodium chloride and reextracted with four 4L portions of methylene chloride which were then combined and dried over magnesium sulfate. The two 16L batches of extracts were combined, filtered and concentrated to dryness under vacuum to give 115.5g of product which contained 1.6% of an impurity identified as 7-iodo-3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one.

A solution of 107.02g (0.607mol) of the intermediate obtained above in 1.712L of ethanol was hydrogenated at room temperature and 40psi over 4.00g of 10% palladium on carbon for 4 hours. The catalyst was removed

by filtration through solkaflok and the filtrate concentrated to dryness under vacuum to give 101.08g (0.574mol, 94.4%) of product.

Step F: N-Chlorosulfonyl-4,4-dimethylazetidin-2-one

To a 3-neck 12L flask equipped with an overhead stirrer, a 250mL addition funnel topped with a nitrogen inlet and a rubber septum to allow a temperature probe and isobutylene needle was charged 450mL of isobutylene. The flask was cooled in a dry ice-acetone bath. Ethyl ether (450mL) was added and the resulting solution at -60°C was treated with 210mL (2.41mol) of chlorosulfonyl isocyanate over 5 minutes at a rate so as to maintain the internal temperature below -50°C. The mixture was stirred at -50°C to -62°C for 30 minutes ther allowed to warm slowly to room temperature and treated with 2250mL of ether. The resulting solution was treated with 750mL of 10% aqueous sodium carbonate slowly in 3 portions. The mixture was transferred into a 4L separatory funnel and the aqueous layer removed. The organic layer was washed with 500mL of water, then removed and treated with 750mL of hexane. As crystallization began, additional hexane (250mL) was added and the mixture concentrated under partial vacuum to a final volume of 3100mL. The solid that formed was removed by filtration with the aid of 200mL of hexane for rinsing. After air drying, the wet cake was dried under vacuum at 40°C overnight to give 253g (1.28mol,53%) of product as a pale yellow crystalline solid. Recycling of the mother liquors gave an additional 100g (19%) of product as a white crystalline solid. ^{1}H NMR (250MHz, $CDCl_3$): 1.89 (s,6H), 3.05 (s,2H).

Step G: 3-methoxysulfonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide

A suspension of 98.31g (0.530mol) of 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one in 1600mL of methanol at room temperature was treated with 155mL (1.112mol) of triethylamine. The resulting suspension was cooled to 0°C and treated with a solution of 110.01g (0.557mol) of N-chlorosulfonyl-4,4-dimethylazetidin-2-one in 960mL of methanol over 20 minutes maintaining the internal temperature below 10°C. Additional methanol (100mL) was used to rinse the flask and the rinse was transferred into the reaction vessel. The reaction mixture was warmed to room temperature and stirred for 90 minutes.

The reaction mixture was concentrated under vacuum to a slurry (600mL) which was diluted with 3180mL of ethyl acetate and treated with 1L of saturated aqueous ammonium chloride and 1L of water. The organic layer was separated, washed with 2L of 1:1 saturated aqueous ammonium chloride/water then 2L of brine. The organic layer was removed and concentrated under vacuum to a final volume of 1.6L. The resulting slurry was treated with 1.6L of hexane and then aged at room temperature for 2.5 hours. The solid was removed by filtration and the cake washed with 1L of hexane. The material was air dried at 40°C for 48 hours to give 163.81g (0.444mol, 83.7%) of product as a white solid.
^{1}H NMR (250MHz,$CDCl_3$): 1.39 (s,3H), 1.42 (s,3H), 2.04 (m,1H), 2.37 (d,15Hz,1H), 2.58 (d,15Hz,1H), 2.69 (m,2H), 2.95 (m,1H), 3.81 (s,3H), 4.55 (m,1H), 6.83 (m,2H), 7.01 (d,8Hz,1H), 7.25 (m,3H), 8.20 (br s,1H).

Step H: 3-Methoxysulfonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]-butanamide

To a suspension of 155.0g (0.4197mol) of the intermediate obtained in Step G in 800mL of tetrahydrofuran was added 140mL of dimethylformamide and the resulting solution cooled to 0° to -5°C and treated with 19.1g of 95% sodium hydride (0.796mol). Additional tetrahydrofuran (40mL) was used to rinse the addition funnel. The mixture was stirred for 30 minutes at 0°C then treated with a solution of 269.0g (0.4825mol) of N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] in 800mL of tetrahydrofuran over 20 minutes. After the addition was complete, the reaction mixture was warmed to room temperature and stirred for 5 hours. An additional 1.0g of 95% sodium hydride was added and stirring continued for another 3.5 hours.

The reaction mixture was poured into a mixture of 3L of ethyl acetate and 2.5L of water. Additional water (300mL) and ethyl acetate (500mL) were used for rinsing. The aqueous layer was removed and the organic layer washed with 2L of brine. The organic layer was separated, dried over sodium sulfate, filtered and concentrated under vacuum to a viscous oil. The oil was further concentrated under vacuum to form a pale yellow solid which was purified by chromatography on silica, eluting with ethyl acetate/hexanes (1:1 to 3:1) to afford 330.6g (0.3908mol, 89.3%) of product as a white solid.

Step I: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(hydrochloride), di(hydrate)

To 900mL of hot (70°C) ethanol was added, with vigorous stirring, 190.0g (0.2246mol) of the intermediate obtained in Step H by a solid addition funnel. Additional ethanol (50mL) was used to rinse the funnel. To the clear solution at 70°C was added 380mL of 6N hydrochloric acid over 10 minutes. The mixture was stirred at 70°C for 4.5 hours then allowed to cool to room temperature. The reaction mixture was poured into a mixture of 1900mL of water and 3L of ethyl acetate/hexane (2:1). The aqueous layer was removed and washed with 3L of ethyl acetate/hexane (2:1) then 2.5L of hexane. The aqueous layer was separated and filtered, then concentrated under vacuum at 40°C to a final volume of 3500mL and allowed to age overnight at ambient temperature. The white suspension was removed by filtration and the wet cake washed with 250mL of a solution of 15mL of concentrated hydrochloric acid in 500mL of water. The product was dried under vacuum at 35-40°C overnight then allowed to equilibrate in ambient humidity to give 110.25g (0.1894mol, 90.7%) of the title compound as a white powdery solid. ^{1}H NMR (250MHz, CD_3OD): 1.36 (s,3H), 1.40 (s,3H), 2.12 (m,1H), 2.30 (m,1H), 2.50 (m,2H), 2.55 (m,2H), 4.36 (dd;8,12Hz;1H), 4.87 (d,15Hz,1H), 5.21 (d,15Hz,1H), 7.00 (m,2H), 7.17 (m,2H), 7.22 (m,2H), 7.31 (m,2H), 7.51 (m,1H), 7.53 (m,1H), 7.61 (m,2H).

Example 114

3-[(2,2-Dimethyl-1,3-dioxolane-4(S)-yl)methyl]amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

To a stirred solution of 116mg (0.20mmol) of 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H -1-benzazepin-3(R)-yl]-butanamide, hydrochloride, dihydrate (Example 113) in 5mL of dry uethanol was added 0.5g of dry 3A powdered molecular sieves followed by a solution of 131mg (1.0mmol) of D-glyceraldehyde acetonide (used crude as prepared according to the procedure of Hertel, L.W.; Grossman, C. S.; Kroin, J.S. Synth. Comm. **1991**, 21, 151-154) in 1mL of dry methanol. The pH of the mixture was carefully adjusted to 6.5 with glacial acetic acid and triethylamine. The reaction was stirred at room temperature for 3 hours at which time 1.0mL (1.0mmol) of a 1.0M solution of sodium cyanoborohydride in tetrahydrofuran was added dropwise by syringe. The reaction was stirred overnight then filtered through a pad of Celite. The filtrate was diluted with 50% aqueous trifluoroacetic acid and stirred for 3 hours at room temperature. The solution was concentrated under vacuum and the residue purified by preparative reverse phase high pressure liquid chromatography on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient; 60% methanol to 85% methanol over 10 minutes). The title compound was thus obtained in addition to the faster eluting major product 3-(2(S),3-dihydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide. ^{1}H NMR (200MHz,CD_3OD): 1.35-1.40 (m,12H), 2.05-2.75 (m,6H), 3.01 (dd;8,12Hz;1H), 3.26 (dd;3,12Hz;1H), 3.78 (dd;5,10Hz;1H), 4.15 (dd;6,8Hz,1H), 4.36 (m,2H), 4.85 (d,15Hz,1H), 5.15 (d,15Hz,1H), 7.03 (d,8Hz,2H), 7.2-7.4 (m,6H), 7.5-7.7 (m,4H).

Example 115

3-(2(S),3-Dihydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, hydrochloride, dihydrate (Example 113) and D-glyceraldehyde acetonide by the procedure described in Example 114.
^{1}H NMR (200MHz,CD_3OD): 1.37 (s,3H), 1.39 (s,3H), 2.05-2.75 (m,6H), 2.95 (dd;8,11Hz;1H), 3.19 (dd;3,11Hz;1H), 3.56 (m,2H), 3.84 (m,1H), 4.35 (dd;8,12Hz,1H), 4.93 (d,15Hz,1H), 5.16 (d,15Hz,1H), 7.04 (d,8Hz,2H), 7.15-7.35 (m,6H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{32}H_{37}N_7O_4$ 583; found 585 (100%).

Example 116

3-(2(S),3(S),4-Trihydroxybutyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-

5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, hydrochloride, dihydrate (Example 113) and 5(S)-t-butyldimethylsilyloxymethyl-2,2-dimethyl-1,3-dioxolan-4(R)-carboxaldehyde (Example 82) by the procedure described in Example 71. ^{1}H NMR (400MHz,CD_3OD): 1.36 (s,3H), 1.40 (s,3H), 2.09 (m,1H), 2.30 (m,1H), 2.46 (m,1H), 2.57 (dd;7,11Hz,1H), 2.64 (s,2H), 3.13 (m,2H), 3.59 (br s,3H), 3.92 (m,1H), 4.35 (dd;7,12Hz;1H), 4.9 (d,15Hz,1H), 5.18 (d,15Hz,1H), 7.02 (d,8Hz,2H), 7.18 (d,8Hz,2H), 7.22 (m,2H), 7.30 (m,2H), 7.53 (m,2H), 7.63 (m,2H). FAB-MS: calculated for $C_{33}H_{39}N_7O_5$ 613; found 614 (100%).

Example 117

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-benzyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

To a stirred solution of 174mg (0.20mmol) of 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(**R**)-yl]-butanamide, hydrochloride, dihydrate (Example 113) in 3mL of tetrahydrofuran and 1mL of dimethylformamide was added 0.22mL (5eq.) of triethylamine followed by 0.043mL (1.2eq.) of benzyl bromide. The mixture was stirred for 2 hours at room temperature then concentrated under vacuum. Initial purification by reverse phase high pressure liquid chromatography on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid (75:25) afforded a major product (1-benzyl isomer) followed by a minor product (2-benzyl isomer). Repurification of each product by reverse phase high pressure liquid chromatography on CI8, eluting with methanol/0.1% aqueous trifluoroacetic acid (70:30) afforded 9mg of the title compound in addition to 8mg of the 2-benzyl isomer.
^{1}H NMR (200MHz,CD_3OD): 1.35 (s,3H), 1.39 (s,3H), 2.05-2.65 (m,6H), 4.38 (dd;7,11Hz;1H), 4.82 (d,15Hz,1H), 4.85 (s,2H), 5.35 (d,15Hz,1H), 6.77 (dd;2,8Hz;2H), 6.94 (d,8Hz,2H), 7.1-7.8 (m,13H). FAB-MS: calculated for $C_{36}H_{37}N_7O_2$ 599; found 601 (100%).

Example 118

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(2-benzyltetrazol-5-yl)[1,1'-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(**R**)-yl]-butanamide, hydrochloride, dihydrate (Example 113) and benzyl bromide by the procedure described in Example 117.
^{1}H NMR (200MHz,CD_3OD): 1.35 (s,3H), 1.39 (s,3H), 2.00-2.65 (m,6H), 4.40 (dd;7,11Hz;1H), 4.88 (d,15Hz,1H), 5.26 (d,15Hz,1H), 5.74 (s,2H), 6.96 (d,8Hz,2H), 7.10 (d,8Hz,2H), 7.25 (m,3H), 7.30-7.65 (m,9H), 7.73 (dd;2,7Hz,1H). FAB-MS: calculated for $C_{36}H_{37}N_7O_2$ 599; found 601 (100%).

Example 119

3-(3(R)-Hydroxybutyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'(1H-tetrazol-5-yl)[[1,1'-biphenyl]-4-yl)methyl]-1H-1-benzazepin-3(R)-yl)-butanamide, trifluoroacetate

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(**R**)-yl]-butanamide, hydrochloride, dihydrate (Example 113) and 3(R)-hydroxybutanal-O-tetrahydropyranyl ether (prepared from methyl 3(R)-hydroxybutyrate by the method of Sato: Heterocycles, 24, 2173 (1986)) by the procedure described in Example 71.
^{1}H NMR (200MHz,CD_3OD): 1.12 (d,6Hz,3H), 1.33 (s,3H), 1.36 (s,3H), 1.70 (m,3H), 2.00-2.60 (m,5H), 3.09 (m,2H), 3.82 (m,1H), 4.34 (dd;7,11Hz;1H), 4.85(d,15Hz,1H), 5.18 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.1-7.3 (m,6H), 7.5-7.7 (m,4H). FAB-MS: calculated for $C_{33}H_{39}N_7O_3$ 581; found 583 (100%).

Example 120

3-(3(S)-Hydroxybutyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(**R**)-yl]-butanamide, hydrochloride, dihydrate (Example 113) and 3(S)-hydroxybutanal-O-tetrahydropyranyl ether (prepared from methyl 3(S)-hydroxybutyrate by the

method of Sato: Heterocycles, 24, 2173 (1986)) by the procedure described in Example 71. ^{1}H NMR (200MHz,CD_3OD): 1.15 (d,6Hz,3H), 1.33 (s,3H), 1.36 (s,3H), 1.70 (m,3H), 1.9-2.6 (m,5H), 3.10 (m,2H), 3.84 (m,1H), 4.33 (dd;8,12Hz,1H), 4.85 (d,15Hz,1H), 5.19 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.10-7.35 (m,6H), 7.45-7.70 (m,4H). FAB-MS: calculated for $C_{33}H_{39}N_7O_3$ 581; found 583 (100%).

Example 121

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[3-bromo-2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl] methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 2-Bromo-4-iodotoluene

A well stirred solution of 18.6g (0.10mol) of 3-bromo-p-toluidine in 80mL of 6N HCl at 0°C was treated with a solution of 7.35g (0.11mol) of sodium nitrite in 15mL of water at a rate that maintained the temperature <10°C. The mixture was stirred for 45 minutes then cautiously treated with 33.2g (0.20mol) of potassium iodide at 0°C. The mixture was treated with 300mL of ether and washed (3x) with saturated aqueous sodium bisulfite. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was redissolved in 50mL of hexane, filtered through 30g of silica and concentrated under vacuum to afford 15.6g (0.053mol,53%) of the product which was determined to be 65% pure by ^{1}H NMR. ^{1}H NMR (200MHz-,$CDCl_3$): 2.33 (s,3H), 6.97 (d,8Hz,1H), 7.51 (dd;2,8Hz,1H), 7.86 (d,2Hz,1H).

Step B: 2′-[(N-Triphenylmethyl)tetrazol-5-yl]-2-bromo-1-methyl-1,1′-biphenyl

A solution of 6.0g (15mmol) of 5-phenyl-2-trityltetrazole (Example 1, Step H) in 60mL of tetrahydrofuran at -15°C to -10°C was treated with 6.5mL of 2.5M n-butyllithium in hexane (16.3mmol,1.05eq) and the resulting mixture stirred for 1.5 hours at -5°C to -10°C then treated with 9.2mL of 1.0M solution of zinc chloride in ether (9.2mmol,0.6eq). The mixture was warmed to room temperature and treated with: 0.3g of bis(triphenylphosphine) nickel dichloride, 0.3mL of a 3M solution of methylmagnesium chloride in tetrahydrofuran and finally, a solution of 8.5g (29mmol) of 2-bromo-4-iodotoluene in 12mL of tetrahydrofuran. The mixture was stirred overnight at room temperature then treated with an additional 1.5g of 2-bromo-4-iodotoluene and heated briefly to 40°C. The mixture was cooled and partitioned between ether and saturated citric acid. The organic layer was separated, washed with brine (2x), dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was dissolved in methylene chloride, passed through a short plug of silica, and concentrated under vacuum. The gummy residue was dissolved in ether and treated with an equal volume of hexane to precipitate the product. By this method, 4.3g (7.7mmol,51%) of product was obtained as a white powder. ^{1}H NMR (400MHz, $CDCl_3$): 2.29 (s,3H), 6.83 (t,8Hz,2H), 6.89 (d,8Hz,6H), 7.2-7.4 (m,11H), 7.45 (m,2H), 7.92 (dd;2,8Hz;1H).

Step C 2′-[(N-Triphenylmethyl)tetrazol-5-yl]-2-bromo-1-bromomethyl-1,1′-biphenyl

Prepared from the intermediate obtained in Step B by the procedure described in Example 69, Step C. ^{1}H NMR (200MHz,$CDCl_3$): 4.48 (s,2H), 6.85-7.05 (m,8H), 7.20-7.55 (m,13H), 8.03 (m,1H). ^{1}H NMR indicates the product thus obtained contains approximately 20% starting material.

Step D: 3-t-Butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[3-bromo-2′-(N-triphenylmethyl)tetrazol-5-yl][1,1′-biphenyl]-4-yl] methyl-1H-1-benzazepin-3(R)-yl]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) and 2′-[(N-triphenylmethyl)tetrazol-5-yl]-2-bromo-1-bromometh yl-1,1′-biphenyl by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz,$CDCl_3$): 1.34 (s,3H), 1.35 (s,3H), 1.40 (s,9H), 1.90 (m,1H), 2.43 (d,14Hz,1H), 2.55 (d,14Hz,1H), 2.5-2.8 (m,3H), 4.57 (m,1H), 4.97 (d,15Hz,1H), 5.14 (d,15Hz,1H), 5.31 (br s,1H), 6.66 (d,7Hz,1H), 6.95-7.15 (m,13H), 7.20-7.40 (m,10H), 7.46 (m,2H), 7.93 (m,1H).

Step E: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[3-bromo-2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step D by the procedure described in Example 31, Step H.

^{1}H NMR (200MHz, CD_3OD): 1.32 (s,3H), 1.37 (s,3H) 2.0-2.9 (m,6H), 4.40 (dd;8,12Hz,1H), 4.90 (d,15Hz,1H), 5.26 (d,15Hz,1H), 6.96 (dd;2,8Hz,1H), 7.10-7.45 (m,6H), 7.45-7.70 (m,4H). FAB-MS: calculated for $C_{29}H_{30}BrN_7O_2$ 587,589; found 589 (98%); 591 (100%).

Example 122

3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[3-bromo-2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, hydrochloride

Step A: 3-[2(R)-Benzyloxypropyl]amino-3-methyl-N-[2, 3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide

Prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 107, Step C) and (R)-2-benzyloxypropanal (prepared from ethyl-D-lactate according to the procedure of Hanessian and Kloss, Tetrahedron Lett. **1985**, 26, 1261-1264.) by the procedure described in Example 86, Step A. ^{1}H NMR (200MHz,CD_3OD): 1.31 (d,6Hz,3H), 1.40 (s,3H), 1.43 (s,3H), 2.17 (m,1H), 2.30 (m,1H), 2.6-3.1 (m,5H), 3.22 (dd;3,12Hz;1H), 3.86 (m,1H), 4.48 (dd;7,12Hz;1H), 4.50 (d,12Hz,1H), 4.70 (d,12Hz,1H), 7.11 (d,8Hz,1H), 7.15-7.45 (m,8H). FAB-MS: calculated for $C_{25}H_{33}N_3O_3$ 423; found 424 (M+H,100%).

Step B: 3-[2(R)-Hydroxypropyl]amino-3-methyl-N-[2,3, 4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

A solution of 750mg (1.40mmol) of the intermediate obtained in Step A in methanol containing 2 drops of trifluoroacetic acid was hydrogenated at room temperature and 40psi in the presence of 300mg of 30% palladium on carbon for 3 days. The catalyst was removed by filtration through Celite and the filtrate concentrated under vacuum to give 600mg (1.34mmol,96%) of product.^{1}H NMR (200MHz, CD_3OD): 1.22 (d,7Hz,3H), 1.37 (s,3H), 1.39 (dd;2,11Hz,1H), 3.93 (m,1H), 4.38 (dd;8,12Hz,1H), 7.05 (d,8Hz,1H), 7.10-7.35 (m,3H).

Step C: 3-[2(R)-Triethylsiloxypropyl]amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide

To a stirred solution of 660mg (1.48mmol) of the intermediate obtained in Step B in 3mL of methylene chloride at room temperature was added 1.1mL of N,N-diisopropylethylamine (0.81g, 4.2eq.) followed by 0.71mL of triethylsilyl trifluoromethanesulfonate (0.83g, 2.1eq.). The resulting mixture was stirred at room temperature for 2 hours then partitioned between ethyl acetate and saturated aqueous sodium chloride (buffered to pH 9 with 2 drops of ammonium hydroxide). The organic layer was separated, washed with buffered brine, dried over magnesium sulfate, filtered and solvents evaporated under vacuum. The residue was purified by preparative high pressure liquid chromatography on silica, eluting with ethyl acetate/0.1% ammonium hydroxide in methanol (85:15), to afford 480mg (1.07mmol,72%) of product. ^{1}H NMR (200MHz,CD_3OD): 0.63 (g,8Hz,6H), 0.97 (t,8Hz,9H), 1.14 (s,6H), 1.18 (d,6Hz,3H), 2.05 (m,1H), 2.28 (d,2Hz,2H), 2.35-3.00 (m,5H), 4.01 (m,1H), 4.44 (dd;8,12Hz;1H), 7.05 (d,8Hz,1H), 7.10-7.35 (m,3H). FAB-MS: calculated for $C_{24}H_{41}N_3O_3Si$ 447; found 448 (M+H,100%).

Step D: 3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[3-bromo-2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl] methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, hydrochloride

To a stirred solution of 94mg (0.21mmol) of the intermediate obtained in Step C in 0.5mL of dimethylformamide was added 6mg of 60% sodium hydride oil dispersion (3.6mg NaH, 1.2eq.). The resulting solution was stirred for 15 minutes then treated with a solution of 201mg (0.31mmol,1.5eq.) of 2'-[(N-Triphenylmethyl)tetrazol-5-yl]-2-bromo-1-bromomethyl-1,1'-biphenyl (Example 121, Step C) in 0.5mL of dimethylformamide. The resulting solution was stirred at room temperature for 2 hours then added to 50mL of ethyl acetate and washed with brine (2x). The organic layer was separated, dried over sodium sulfate, filtered and solvents removed under vacuum.

The residue was dissolved in 2mL of methanol and treated with 10mL of 9N HCl and 10mL of hexane. This mixture was stirred vigorously for 2 hours then the layers allowed to separate. The aqueous layer was removed by pipet, washed once with hexane, filtered and evaporated under vacuum. The residue was triturated with methanol to give a white solid that was removed by filtration. Thus, 101mg (0.15mmol,71%) of the title compound

was obtained as a white solid. ^{1}H NMR (300MHz,CD_3OD): 1.23 (d,6Hz,3H), 1.40 (s,3H), 1.41 (s,3H), 2.24 (m,1H), 2.40 (m,1H), 2.61 (d,15Hz,1H), 2.69 (d,15Hz,1H), 2.7-3.0 (m,5H), 3.13 (dd;3,11Hz;1H), 3.96 (m,1H), 4.47 (dd;7,12Hz;1H), 4.9 (d,15Hz,1H), 5.38 (d,15Hz,1H), 7.17 (d,8Hz,2H), 7.25-7.40 (m,3H), 7.45 (d,8Hz,1H), 7.48 (d,2Hz,1H), 7.64 (m,2H), 7.74 (m,2H). FAB-MS: calculated for $C_{32}H_{36}BrN_7O_3$ 645,647; found 646(50%), 648(55%).

Example 123

3′-Bromo-4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl) amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl] methyl][1,1′-biphenyl]-2-carboxamide, trifluoroacetate

Step A: 3′-Bromo-4′-methyl-1,1′-biphenyl-2-nitrile

A solution of 5.2g (27mmol) of 4′-methyl-1,1′-biphenyl-2-nitrile (Example 69, Step B) in 60mL of methylene chloride at 0°C was treated with 6.7g of silver trifluoroacetate (30mmol). When all the silver trifluoroacetate was dissolved, 1.6mL of bromine was added dropwise (4.95g, 31mmol) with vigorous stirring. After two hours, the reaction mixture was filtered and the solid washed with methylene chloride. The combined organic layers were washed once with dilute (<1N) aqueous sodium hydroxide and once with brine. The organic layer was removed, dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by preparative high pressure liquid chromatography on silica, eluting with 10% ether/hexane to give 3g (41%) of product. ^{1}H NMR (200MHz,$CDCl_3$): 2.46 (s,3H), 7.2-7.8 (m,7H).

Step B: 3′-Bromo-4′bromomethyl-1,1′-biphenyl-2-nitrile

Prepared from the intermediate obtained in Step A by the procedure described in Example 69, Step C. NMR analysis shows product to contain small amounts of starting material and dibromomethyl compound. ^{1}H NMR (200MHz,$CDCl_3$): 4.64 (s,2H), 7.4-7.8 (m,7H). FAB-MS: calculated for $C_{14}H_9Br_2N$ 351; found 352 (100%); 271 (100%)

Step C: 3-[[1-[[3-Bromo-2′-cyano-[1,1′-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-2-oxo-1H-benza zepin-3(R)-yl]amino]-1,1-dimethyl-3-oxo-propylcarbamic acid, 1,1-dimethylethyl ester

Prepared from 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) and 3′-bromo-4′-bromomethyl-1,1′-biphenyl-2-nitrile by the procedure described in Example 69, Step D. ^{1}H NMR (200MHz,$CDCl_3$): 1.33 (s,3H), 1.34 (s,3H), 1.40 (s,9H), 1.91 (m,1H), 2.43 (d,14Hz,1H), 2.55 (d,14Hz,1H), 2.55-2.90 (m,3H), 4.62 (m,1H), 4.95 (d,16Hz,1H), 5.28 (s,1H), 5.34 (d,16Hz,1H), 6.63 (d,7Hz,1H), 7.10-7.25 (m,4H), 7.45 (m,4H), 7.64 (m, 1H), 7.75 (m,2H). FAB-MS (Li spike): calculated for $C_{34}H_{37}BrN_4O_4$ 644, 646; found 651 (13%); 653 (15%).

Step D: 3′-Bromo-4′-[[3(R)-[(3-t-butoxycarbonylamino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1, 1′-bipenyl]-2-carboxamide

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 69, Step E. ^{1}H NMR (200MHz, $CDCl_3$): 1.34 (br s,6H), 1.40 (s,9H), 1.93 (m,1H), 2.43 (d,13Hz,1H), 2.56 (d,13Hz,1H), 2.55-2.90 (m,3H), 4.62 (m,1H), 4.96 (d,16Hz,1H), 5.30 (d,16Hz,1H), 5.34 (br s,1H), 5.65 (br s,1H), 6.69 (d,7Hz,1H), 7.05-7.55 (m,9H), 7.63 (s,1H), 7.71 (dd;2,8Hz;1H). FAB-MS: calculated for $C_{34}H_{39}BrN_4O_5$ 662, 664; found 663 (2%); 665 (3%).

Step E: 3′-Bromo-4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step D by the procedure described in Example 69, Step F. ^{1}H NMR (200MHz,CD_3OD): 1.35 (s,3H), 1.37 (s,3H), 2.10-3.00 (m,6H), 4.48 (dd;8,12Hz;1H), 4.93 (d,16Hz,1H), 5.33 (d,16Hz,1H), 7.15-7.60 (m,10H), 7.67 (d,2Hz,1H). FAB-MS: calculated for $C_{29}H_{31}BrN_4O_3$ 562, 564; found 563 (38%); 565 (37%).

Example 124

3'-Bromo-4'-[[3(R)-[[3-[(2(S),3-dihydroxypropyl) amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from 3'-bromo-4'-[[3(R)-[(3-amino-3-methyl-1-oxo-butyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]m ethyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate (Example 123) and D-glyceraldehyde acetonide by the procedure described in Example 71. ^{1}H NMR (200MHz, CD_3OD): 1.36 (s, 6H), 2.1-3.0 (m, 6H), 3.17 (dd;4,12Hz;1H), 3.50 (m,2H), 3.83 (m,1H), 4.46 (dd;8,12Hz;1H), 4.82 (d,16Hz,1H), 5.40 (d,16Hz,1H), 7.10-7.60 (m,10H), 7.70 (s,1H). FAB-MS: calculated for $C_{32}H_{37}BrN_4O_5$ 636, 638; found 637 (35%); 639 (35%).

Example 125

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-carbomethoxy-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

Step A: 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-carbomethoxy-[1,1'-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3-yl]butanamide

Prepared from 3-benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide (Example 51, Step A) and methyl 4'-bromomethyl-1,1'-biphenyl-2-carboxylate (prepared by the method of D. J. Carini, et al, EPO publication 324,377) by the procedure described in Example 1, Step K. ^{1}H NMR (300MHz,$CDCl_3$): 1.37 (s,3H), 1.39 (s,3H), 1.75 (m,1H), 2.3-2.6 (m,5H), 3.52 (s,3H), 4.50 (m,1H), 4.80 (d,14Hz,1H), 5.06 (s,2H), 5.34 (d,14Hz,1H), 5.65 (s,1H), 6.72 (d,7Hz,1H), 7.1-7.4 (m,15H), 7.48 (dt;2,8Hz;1H), 7.78 (dd;2,8Hz;1H). FAB-MS: calculated for $C_{38}H_{39}N_3O_6$ 633; found 634 (M+H,60%).

Step B: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-carbomethoxy-[1,1'-biphenyl]-4-yl] methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 1, Step L. ^{1}H NMR (300MHz, CD_3OD): 1.40 (s,3H), 1.44 (s,3H), 2.17 (m,1H), 2.38 (m,1H), 2.5-2.7 (m,4H), 3.56 (s,3H), 4.46 (dd;8,12Hz;1H), 4.98 (d,15Hz,1H), 5.37 (d,15Hz,1H), 7.22 (d,8Hz,2H), 7.25-7.50 (m,8H), 7.59 (dt;2,8Hz;1H), 7.78 (dd;2,8Hz;1H). FAB-MS: calculated for $C_{30}H_{33}N_3O_4$ 499; found 500 (M+H,100%).

Example 126

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-cyano-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

Step A: 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-cyano-[1,1'-biphenyl]4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide (Example 51, Step A) and 4'-bromomethyl-1,1-biphenyl-2-nitrile (Example 69, Step C) by the procedure described in Example 1, Step K. FAB-MS: calculated for $C_{37}H_{36}N_4O_4$ 600; found 601 (M+H,100%).

Step B: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-cyano-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 1, Step L.^{1}H NMR (300MHz,CD_3OD): 1.40 (s,3H), 1.43 (s,3H), 2.18 (m,1H), 2.38 (m,1H), 2.5-2.7 (m,4H), 4.47 (dd;8,12Hz;1H), 5.11 (d,15Hz,1H), 5.28 (d,15Hz,1H), 7.30 (m,2H), 7.35-7.65 (m,8H), 7.76 (dt;2,8Hz;1H), 786 (dd;2,8Hz;1H). FAB-MS: calculated for $C_{29}H_30N_4O_2$ 466; found 467 (M+H,100%).

Example 127

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-trifluoromethyl-[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

Step A: 2-Trifluoromethyl-4′-methyl-1.1′-biphenyl

A solution of 388mp (1.52mmol,1.4eq.) of 4-methylphenyltrimethylstannane (Example 69, Step A) in 5mL of toluene under a nitrogen atmosphere was treated with 238mg of 2-bromobenzotrifluoride (1.06mmol) and 64mg of tetrakis(triphenylphosphine) palladium(0) and the resulting solution heated at reflux for 14 hours. The mixture was cooled, filtered and concentrated under vacuum to give an amber oil that was chromatographed on silica, eluting with hexane, to give the product. ^{1}H NMR (300Hz,$CDCl_3$): 2.41 (s,3H), 7.2-7.8 (m,8H). EI-MS: calculated for $C_{14}H_{11}F_3$ 236; found 236 (M^+,100%).

Step B: 4′-Bromomethyl-2-trifluoromethyl-1,1′-biphenyl

Prepared from 2-trifluoromethyl-4′-methyl-1,1′-biphenyl by the procedure described in Example 69, Step C. EI-MS: calculated for $C_{14}H_{10}BrF_3$ 314,316; found 314 (5%),316 (5%).

Step C: 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-trifluoromethyl-[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]butanamide

Prepared from 3-benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide (Example 51, Step A) and 4′-bromomethyl-2-trifluoromethyl-1,1-biphenyl by the procedure described in Example 1, Step K. ^{1}H NMR (300MHz,$CDCl_3$): 1.37 (s,3H), 1.39 (s,3H), 1.73 (m,1H), 2.2-2.6 (m,5H), 4.50 (m,1H), 4.82 (d,15Hz,1H), 5.06 (s,2H), 5.29 (d,15Hz,1H), 5.65 (s,1H), 6.70 (d,7Hz,1H), 7.1-7.4 (m,14H), 7.44 (t,8Hz,1H), 7.52 (t,8Hz,1H), 7.71 (d,8Hz,1H). FAB-MS: calculated for $C_{37}H_{36}F_3N_3O_4$ 643; found 644 (M+H,55%).

Step D: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-trifluoromethyl-[1,1′-biphenyl]-4-yl] methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

The intermediate obtained in Step C (92mg, 0.14mmol) was treated with 1.62mL of 30% hydrogen bromide in acetic acid at room temperature for 2 hours. The mixture was concentrated under vacuum to give a dark yellow residue. Purification by preparative reverse phase high pressure liquid chromatography on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 75% methanol increased to 85% over 10 minutes) afforded 71mg (0.11mmol, 81%) of the title compound as a colorless glass.
^{1}H NMR (300MHz,CD_3OD): 1.39 (s,3H), 1.44 (s,3H), 2.16 (m,1H), 2.38 (m,1H), 2.5-2.7 (m,4H), 4.47 (dd;8,12Hz;1H), 5.04 (d,15Hz,1H), 5.34 (d,15Hz,1H), 7.20-7.45 (m,9H), 7.56 (t,8Hz,1H), 7.66 (t,8Hz,1H), 7.79 (d,8Hz,1H). FAB-MS: calculated for $C_{29}H_{31}F_3N_3O_2$ 509; found 510 (M+H,100%).

Example 128

3-Amino-3-methyl-N-[7-methylthio-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl] methyl]-1H-1-benzazepin-3-yl]-butanamide, hydrochloride

Step A: 6-Methylthio-1-tetralone oxime

Prepared from 6-methylthio-1-tetralone (prepared by the method described in EPO 0 325, 963 Al) by the procedure described in Example 113, Step A. ^{1}H NMR (200MHz, $CDCl_3$): 1.89 (m,2H), 2.52 (s, 3H), 2.78 (m,4H), 7.02 (d,2Hz,1H), 7.08 (dd;2,8Hz;1H), 7.81 (d,8Hz,1H).

Step B: 7-Methylthio-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 6-methylthio-1-tetralone oxime by the procedure described in Example 113, Step B. ^{1}H NMR (200MHz,$CDCl_3$): 2.23 (m,2H), 2.36 (m,2H), 2.49 (s,3H), 2.78 (t,8Hz,2H), 6.94 (d,8Hz,1H), 7.14 (m,2H), 7.75 (br s,1H).

Step C: 3-Iodo-7-methylthio-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 7-methylthio-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step B. ^{1}H NMR (200MHz,$CDCl_3$): 2.51 (s,3H), 2.6-2.9 (m,3H), 2.50 (s,3H), 2.97 (m,1H), 4.68 (t,9Hz,1H), 6.95 (d,8Hz,1H), 7.15 (m,2H), 7.5 (br s,1H).

Step D: 3-Amino-7-methylthio-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

A mixture of 0.5g of 3-iodo-7-methylthio-2,3, 4,5-tetrahydro-1H-1-benzazepin-2-one and 15g of ammonia in 20mL of chloroform was shaken in a bomb at 100°C for 3 hours. The bomb was cooled, vented and the contents transferred to a separatory funnel. The mixture was washed with water, dried over magnesium sulfate, filtered and solvents removed under vacuum to give the product. ^{1}H NMR (200MHz, $CDCl_3$): 1.90 (m,1H), 2.3-2.7 (m,2H), 2.45 (s,3H), 2.85 (m,1H), 3.39 (dd;8,11Hz;1H), 6.89 (d,8Hz,1H), 7.10 (m,2H), 8.3 (br s,1H).

Step E: 3-t-Butoxycarbonylamino-3-methyl-N-[7-methylthio-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step D and 3-t-butoxycarbonylamino-3-methyl-butanoic acid (Example 31, Step E) by the procedure described in Example 1, Step F. ^{1}H NMR (200MHz,$CDCl_3$): 1.33 (s,6H), 1.40 (s,9H), 1.91 (m,1H), 2.4-3.0 (m,5H), 2.48 (s,3H), 4.50 (m,1H), 5.22 (br s,1H), 6.68 (d,7Hz,1H), 6.90 (d,8Hz,1H), 7.11 (m,2H), 7.66 (br s,1H).

Step F: 3-t-Butoxycarbonylamino-3-methyl-N-[7-methyl thio-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(N-tri phenylmethyl)-tetrazol-5-yl][1,1′-biphenyl]4-yl]methyl-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step E by the procedure described in Example 1, Step K. ^{1}H NMR (200MHz, $CDCl_3$): 1.37 (s,6H), 1.43 (s,9H), 1.78 (m,1H), 2.2-2.7 (m,5H), 2.44 (s,3H), 4.49 (m,1H), 4.69 (d,15Hz,1H), 5.12 (d,15Hz,1H), 5.34 (br s,1H), 6.69 (d,7Hz,1H), 6.9-7.1 (m,12H), 7.2-7.5 (m,13H), 7.87 (m,1H).

Step G: 3-Amino-3-methyl-N-[7-methylthio-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl) [1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, hydrochloride

The title compound was prepared from the intermediate obtained in Step F by the procedure described in Example 34, Step K. ^{1}H NMR (200MHz, DMSO-d_6): 1.24 (s,3H), 1.25 (s,3H), 2.0-2.6 (m,6H), 2.47 (s,3H), 4.25 (m,1H), 4.78 (d,15Hz,1H), 5.15 (d,15Hz,1H), 6.97 (d,8Hz,2H), 7.05-7.30 (m,5H), 7.45-7.70 (m,4H), 7.92 (br s,2H), 8.68 (d,7Hz,1H).

Example 129

3-Amino-3-methyl-N-[7-methylsulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, hydrochloride

Step A: 3-t-Butoxycarbonylamino-3-methyl-N-[7-methylsulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(N-triphenylmethyl)-tetrazol-5-yl][1,1′-biphenyl]-4-yl]methyl-1H-1-benzazepin-3-yl]butanamide

Prepared as a mixture of two racemic diastereomers from the intermediate obtained in Example 128, Step F by the procedure described in Example 48, Step A. ^{1}H NMR (200MHz,$CDCl_3$): 1.37 (s,6H), 1.44 (s,9H), 1.90 (m,1H), 2.4-2.9 (m,5H), 2.78 (s,3H), 4.54 (m,1H), 4.76 (two doublets,15Hz,total of 1H), 5.18 (two doublets,15Hz,total of 1H), 5.32 (br s,1H), 6.9-7.1 (m,9H), 7.2-7.6 (m,15H), 7.90 (m,1H), 7.98 (d,8Hz,1H), 8.08 (br s,1H).

Step B: 3-Amino-3-methyl-N-[7-methylsufinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1, 1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, hydrochloride

The title compound was prepared as a mixture of two racemic diastereomers from the intermediate obtained in Step A by the procedure described in Example 34, Step K.
^{1}H NMR (200MHz,DMSO-d_6): 1.24 (s,3H), 1.26 (s,3H), 2.0-2.8 (m,6H), 2.78 (s,3H), 4.25 (m,1H), 4.94 (d,15Hz,1H), 5.19 (d,15Hz,1H), 7.01 (d,8Hz,2H), 7.16 (d,8Hz,2H), 7.5-7.7 (m,7H), 7.95 (br s,2H), 8.75

(d,7Hz,1H).

Example 130

3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

Step A: 3-Methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl] methyl]-1H-1-benzazepin-3(R)-yl]but-2-eneamide

To a suspension of 1.18g (2.64mmol) of 3(R)-amino-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one, hydrochloride (Example 4, Step C) in 30mL of methylene chloride under nitrogen at -15°C was added 0.923mL (2.64mmol) of triethylamine followed by 0.294mL (2.64mmol) of 3,3-dimethylacryloyl chloride. The reaction mixture was stirred at -15°C for 2 hours then quenched by the addition of 1N hydrochloric acid. The mixture was diluted with 50mL of methylene chloride and washed with 50mL of 1N hydrochloric acid and brine. The organic layer was removed and concentrated to dryness under vacuum. The residue was redissolved in 30mL of methanol and treated with 1.5mL of 9N hydrochloric acid. After stirring for 30 minutes, the mixture was concentrated to dryness under vacuum to give 1.3g (2.63mmol, 99%) of the product as a white solid.

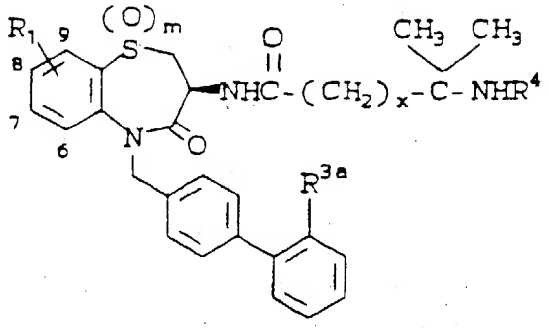
^{1}H NMR (400MHz,CD_3OD): 1.85 (s,3H), 2.06 (s,3H), 2.08 (m,1H), 2.29 (m,1H), 2.44 (m,1H), 2.55 (m,1H), 4.40 (dd;7,11Hz;1H), 4.85 (d,15Hz,1H), 5.26 (d,15Hz,1H), 5.77 (s,1H), 7.00 (d,8Hz,2H), 7.18 (d,8Hz,2H), 7.2-7.4 (m,4H), 7.54 (m,2H), 7.64 (m,2H).

Step B: 3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2, 3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The intermediate obtained in Step A (18mg, 0.037mmol) was dissolved in 2mL of (R)-(-)-1-amino-2-propanol and the resulting solution heated under nitrogen at 120°C for 5 hours. The reaction mixture was cooled, concentrated under vacuum at 50°C and the residue purified by medium pressure liquid chromatography on C8, eluting with methanol/0.1% aqueous trifluoroacetic acid (50:50), to give 14mg (0.021mmol,57%) of the title compound as a colorless glass. The material thus obtained was identical by 400MHz NMR (CD_3OD), FAB-MS and reverse phase analytical high pressure liquid chromatography to the material obtained in Example 102.

Example A

Utilizing the general procedures described in Example 1 to 130, the following compounds of Formula I can be prepared from the appropriately substituted starting materials and reagents.



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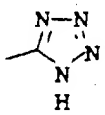
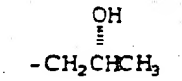
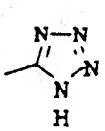
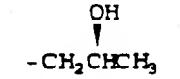
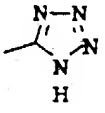
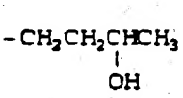
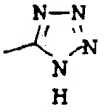
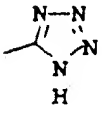
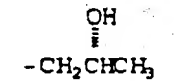
H			1	0
H			1	0
H			1	0
H		H	0	0
H			1	1

Example A (Cont'd)

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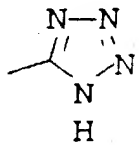
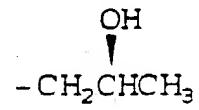
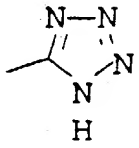
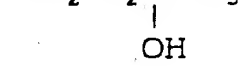
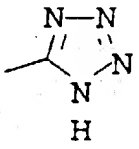
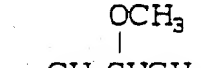
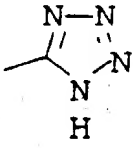
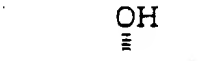
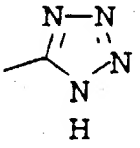
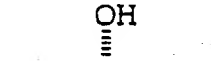
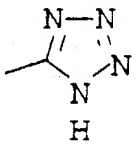
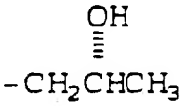
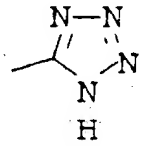
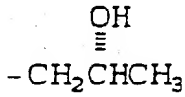
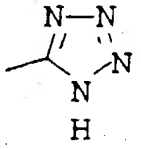
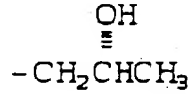
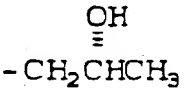
H			1	1
H			1	1
H			1	0
8-F			1	0
8-CF_3			1	0

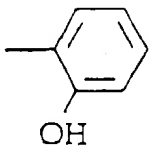
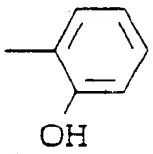
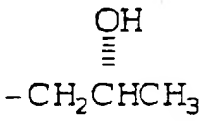
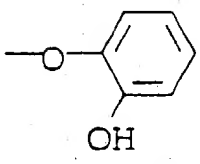
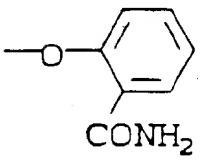
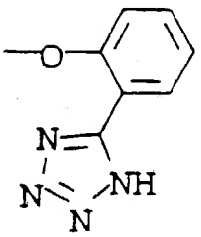
Example A (Cont'd)

R_1	R^{3a}	R^4	x	m
9-F			1	0
8-OCH_3			1	0
8-SCH_3			1	0
H	$-CO_2NH_2$	H	1	0
H	$-CO_2NH_2$	H	1	1
H	$-CO_2NH_2$		1	0

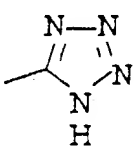
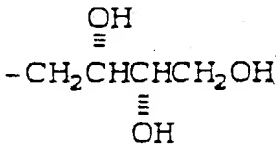
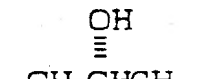
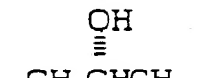
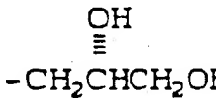
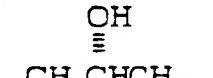
Example A (Cont'd)

R_1	R^{3a}	R^4	x	m
H	$-CO_2NH_2$	$-CH_2\overset{\overset{OH}{\equiv}}{C}HCH_2OH$	1	0
H	$-CO_2NHEt$	H	1	0
H	$-CO_2NHEt$	$-CH_2\overset{\overset{OH}{\equiv}}{C}HCH_3$	1	0
H	$-CO_2NHEt$	$-CH_2\overset{\overset{OH}{\equiv}}{C}HCH_2OH$	1	0
H	$-CH_2CONH_2$	$-CH_2\overset{\overset{OH}{\equiv}}{C}HCH_3$	1	0
H	$-CH_2CONHEt$	$-CH_2\overset{\overset{OH}{\equiv}}{C}HCH_2OH$	1	0

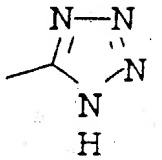
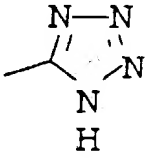
Example A (Cont'd)

R_1	R^{3a}	R^4	x	m
H		H	1	0
H			1	0
H		H	1	0
H		H	1	0
H		H	1	0

Example A (Cont'd)

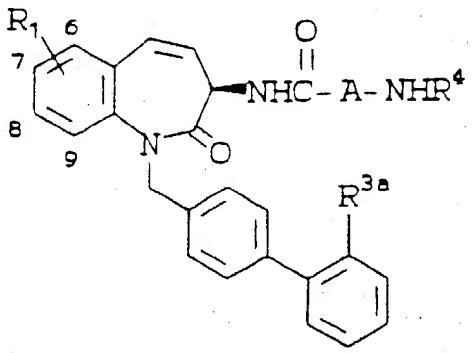
R_1	R^{3a}	R^4	x	m
H			1	0
H	$-CONH_2$	H	0	0
H	-CONHEt	H	0	0
H	$-CH_2OH$	H	1	0
H	$-CH_2OH$		1	0
H	$-CH_2OH$		1	1
H	$-CH_2OH$		1	0
H	$-CH_2NH_2$		1	0
H	$-CH_2NHCOCH_3$	H	1	0

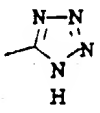
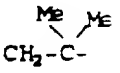
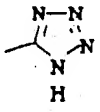
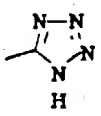
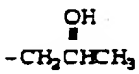
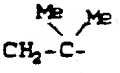
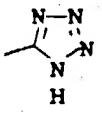
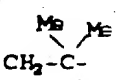
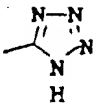
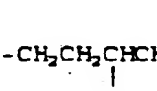
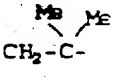
Example A (Cont'd)

R_1	R^{3a}	R^4	x	m
H	$-CH_2NHCOPh$	H	1	0
H	$-CH_2NHCOCH_3$	$-CH_2\overset{\overset{OH}{\equiv}}{C}HCH_3$	1	0
H	$-CH_2NHCOCH_3$	$-CH_2\overset{\overset{OH}{\equiv}}{C}HCH_2OH$	1	0
H		$-CH_2\overset{OH}{\overset{\vert}{C}}(CH_3)_2$	1	0
H		$-CH_2\overset{OH}{\overset{\vert}{C}}(CH_3)_2$	1	1
H	$-CONHOH$	$-CH_2\overset{\overset{OH}{\equiv}}{C}HCH_3$	1	0

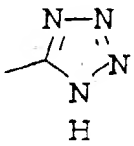
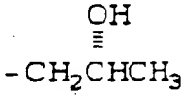
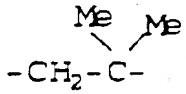
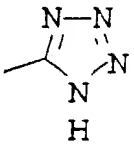
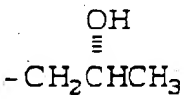
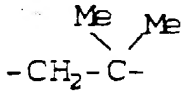
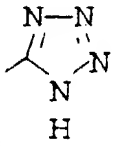
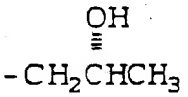
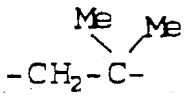
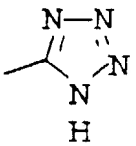
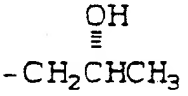
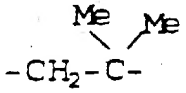
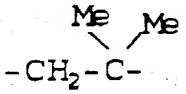
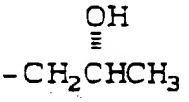
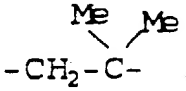
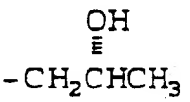
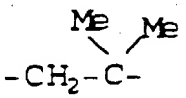
Example B

Utilizing the general procedures described in Example 1 to 130, the following compounds of Formula I can be prepared from the appropriately substituted starting materials and reagents.

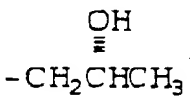
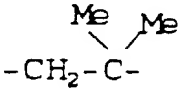
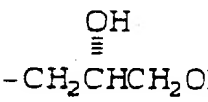
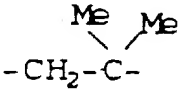
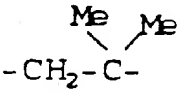
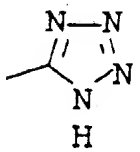
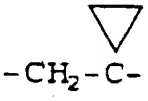
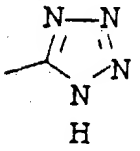
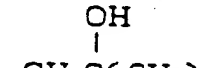
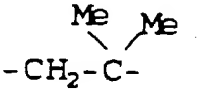


R_1	R^{3a}	R^4	A
H		H	
H		H	
H			
H			
H			

Example B (Cont'd)

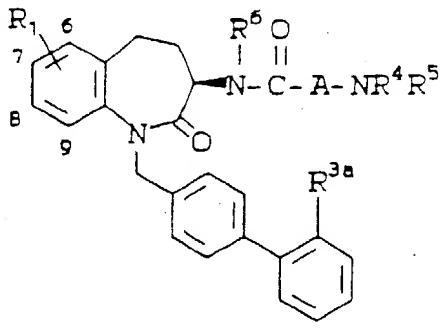
R_1	R^{3a}	R^4	A
7-F			
7-SCH_3			
7-S(O)CH_3			
7-OCH_3			
H	$-CONH_2$	H	
H	$-CONH_2$		
H	-CONHMe		

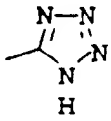
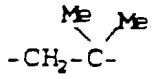
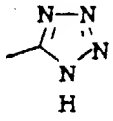
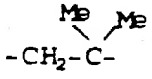
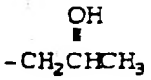
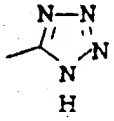
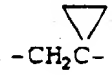
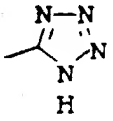
Example B (Cont'd)

R_1	R^{3a}	R^4	A
H	-CONHEt		
H	-CONHEt		
H	-CONHEt	H	
H	-CONHEt	H	
H		H	
H			

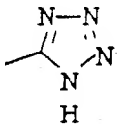
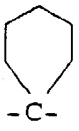
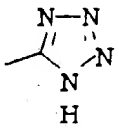
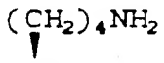
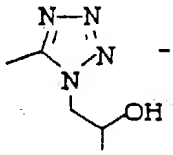
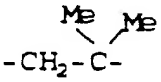
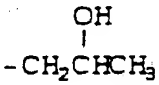
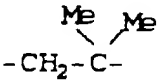
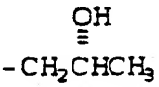
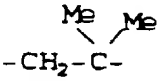
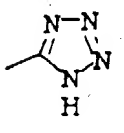
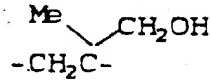
Example C

Utilizing the general procedures described in Example 1 to 130, the following compounds of Formula I can be prepared from the appropriately substituted starting materials and reagents.

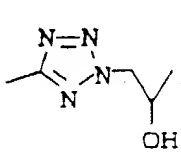
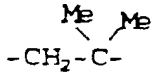
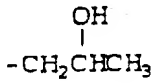
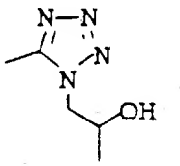
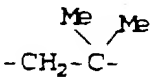
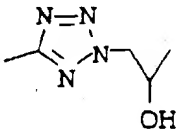
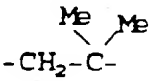
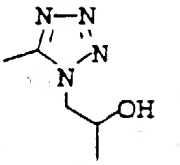
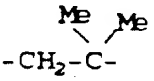
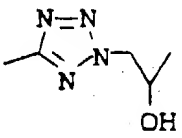
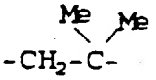
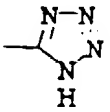


R_1	R^{3a}	A	R^4	R^5	R^6
7-F			H	H	CH_3
H				H	CH_3
H			H	H	H
H			H	H	H

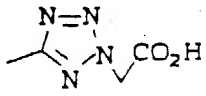
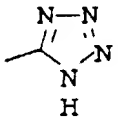
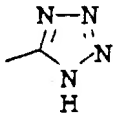
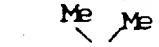
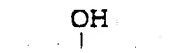
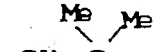
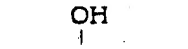
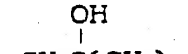
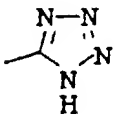
Example C (Cont'd)

R_1	R^{3a}	A	R^4	R^5	R^6
H			H	H	H
H			H	H	H
H				H	H
H	$-C\equiv N$			H	H
H	$-CF_3$		H	H	H
H			H	H	H

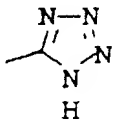
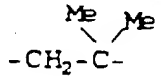
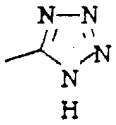
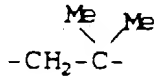
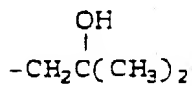
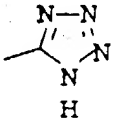
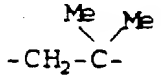
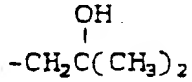
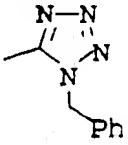
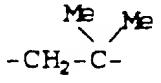
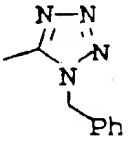
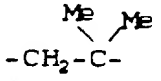
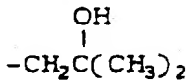
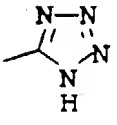
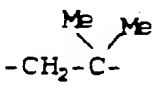
Example C (Cont'd)

R_1	R^{3a}	A	R^4	R^5	R^6
H				H	H
7-F			H	H	H
7-F			H	H	H
H			$-CH_2CH_2OH$	H	H
H			$-CH_2CH_2OH$	H	H
H			H	H	H

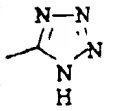
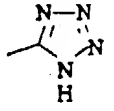
Example C (Cont'd)

R_1	R^{3a}	A	R^4	R^5	R^6
H			H	H	H
H			H	CH_3	H
H				H	H
H	$-CONH_2$			H	H
H	-CONHEt			H	H
7-OCH_3			H	H	H

Example C (Cont'd)

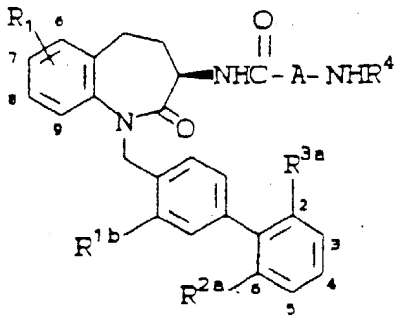
R_1	R^{3a}	A	R^4	R^5	R^6
7-OH			H	H	H
7-OCH_3				H	H
7-OH				H	H
H			H	H	H
H				H	H
H			$-CH_2CH_2OCH_2CH_2-$		H

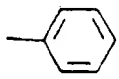
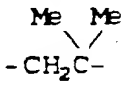
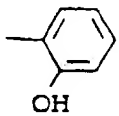
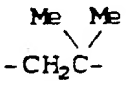
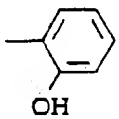
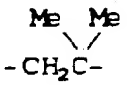
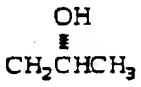
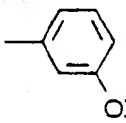
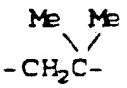
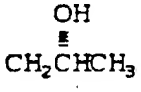
Example C (Cont'd)

R_1	R^{3a}	A	R^4	R^5	R^6
H	-CONHCH$_3$	-CH$_2$C(Me)$_2$-	-CH$_2$CH(OH)CH$_3$	H	H
H	-CONHEt	-C(Me)$_2$-	-CH$_2$CH$_2$CH(OH)CH$_3$	H	H
H	-CONHOH	-C(Me)$_2$-	-CH$_2$CH$_2$CH(OH)CH$_3$	H	H
H	-CONHOH	-CH$_2$C(Me)$_2$-	-CH$_2$CH$_2$CH(OH)CH$_3$	H	H
H		-C(Me)$_2$-	-CH$_2$CH$_2$CH(OH)CH$_3$	H	H
H		-CH$_2$C(Me)$_2$-	-CH$_2$CH$_2$CH(OH)CH$_3$	H	H
H	-CONHOH	-CH$_2$C(Me)$_2$-	-CH$_2$CH(OH)CH$_3$	H	H
7-F	-CONHOH	-CH$_2$C(Me)$_2$-	-CH$_2$CH(OH)CH$_3$	H	H

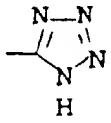
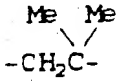
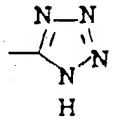
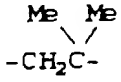
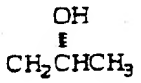
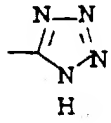
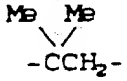
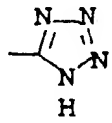
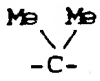
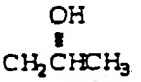
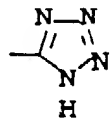
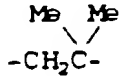
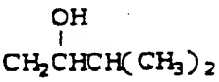
EXAMPLE D

Utilizing the general procedures described in Example 1 to 130, the following compounds of Formula I can be prepared from the appropriately substituted starting materials and reagents.

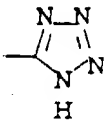
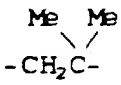
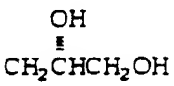
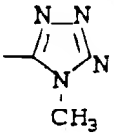
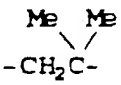
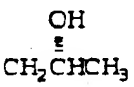
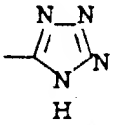
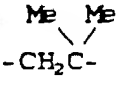
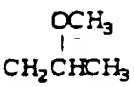
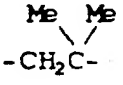


R_1	R^{1b}	R^{2a}	R^{3a}	A	R^4
H	H		H		H
H	H		H		H
H	H		H		
H	H		H		

EXAMPLE D (Cont'd)

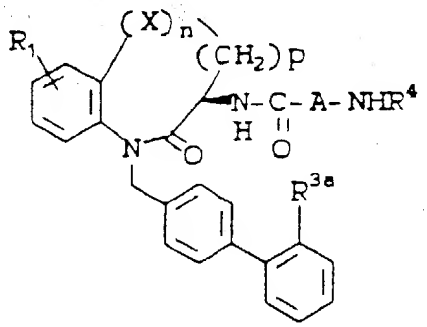
R_1	R^{1b}	R^{2a}	R^{3a}	A	R^4
H	Br	H			H
H	Br	H			
H	H	H			H
H	H	H			
H	H	H			

EXAMPLE D (Cont'd)

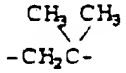
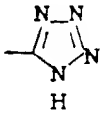
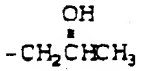
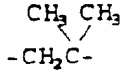
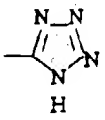
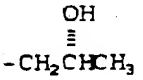
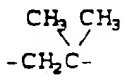
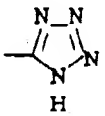
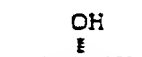
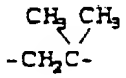
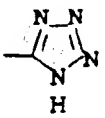
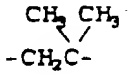
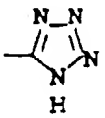
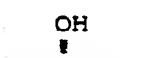
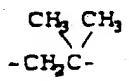
R_1	R^{1b}	R^{2a}	R^{3a}	A	R^4
H	H	H			
H	H	H			
H	H	H			
H	Br	H	$-CONH_2$		H

EXAMPLE E

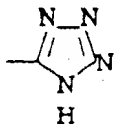
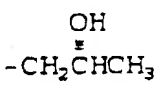
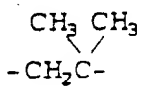
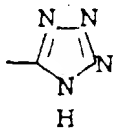
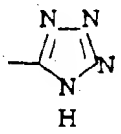
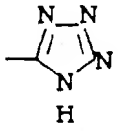
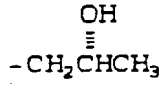
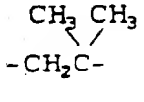
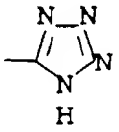
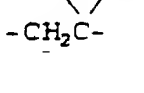
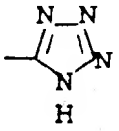
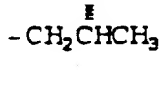
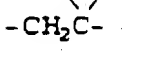
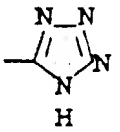
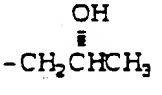
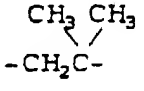
Utilizing the general procedures described in Example 1 to 130, the following compounds of Formula I can be prepared from the appropriately substituted starting materials and reagents.



EXAMPLE E (Cont'd)

X	n	p	R^{3a}	R^4	A
-	o	3		H	
-	o	3			
-	o	1			
-	o	o			
S	1	o		H	
S	1	o			

EXAMPLE E (Cont'd)

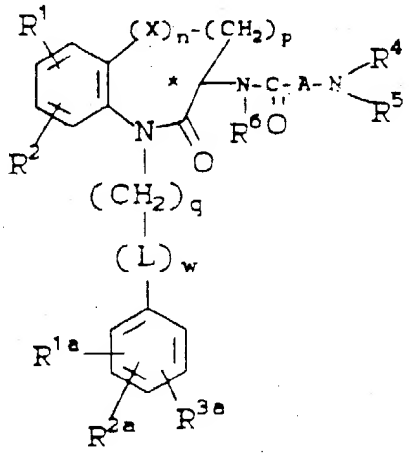
X	n	p	R^{3a}	R^4	A
SO	1	0			
S	1	0			
SO	1	0			
O	1	1			
O	1	1			
C=O	1	1			
CHOH	1	1			

EXAMPLE E (Cont'd)

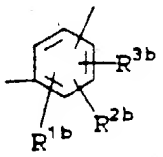
X	n	p	R^{3e}	R^4	A
S	1	0	$-CONH_2$	$-CH_2\overset{\overset{OH}{\vert}}{C}HCH_3$	$-CH_2\overset{\overset{CH_3\ CH_3}{\diagdown\ \diagup}}{C}-$
S	1	0	$-CONHEt$	$-CH_2\overset{\overset{OH}{\vert}}{C}HCH_3$	$-CH_2\overset{\overset{CH_3\ CH_3}{\diagdown\ \diagup}}{C}-$
S	1	0	$-CONHEt$	$-CH_2\overset{\overset{OH}{\vert}}{C}HCH_2OH$	$-CH_2\overset{\overset{CH_3\ CH_3}{\diagdown\ \diagup}}{C}-$
SO	1	0	$-CONHEt$	$-CH_2\overset{\overset{OH}{\vert}}{C}HCH_2OH$	$-CH_2\overset{\overset{CH_3\ CH_3}{\diagdown\ \diagup}}{C}-$
S	1	0	$-CONHOH$	$-CH_2\overset{\overset{OH}{\vert}}{C}HCH_3$	$-CH_2\overset{\overset{CH_3\ CH_3}{\diagdown\ \diagup}}{C}-$
O	1	1	$-CONHEt$	$-CH_2\overset{\overset{OH}{\vert}}{C}HCH_3$	$-CH_2\overset{\overset{CH_3\ CH_3}{\diagdown\ \diagup}}{C}-$

Claims

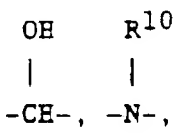
1. A compound having the formula:



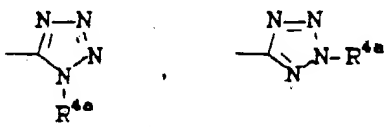
where L is



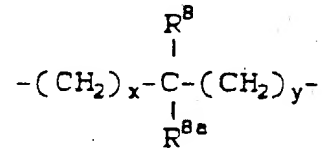
n is 0 or 1;
p is 0 to 3;
q is 0 to 4;
w is 0 or 1;
X is C=O, O, $S(O)_m$,



-CH=CH-;
m is 0 to 2;
R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_3 perfluoroalkoxy, $-S(0)_mR^{7a}$, cyano, nitro, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;
R^{7a} and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, subsituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the phenyl substitutents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy and v is 0 to 3;
R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9 or phenoxy substituted with R^9;
R^9 is

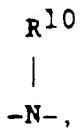


$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-,
$R^{7b}CON(CH_2)_v$-, $R^{7b}O(CH_2)_vCO$-, $R^4R^5N(CH_2)_v$-,
$R^{7b}CON(R^4)(CH_2)_v$-, $R^4R^5NCO(CH_2)_v$-, $R^4R^5NCS(CH_2)_v$-,
$R^4R^5NN(R^5)CO(CH_2)_v$-, $R^4R^5NN(R^5)CS(CH_2)_v$-,
$R^{7b}CON(R^4)N(R^5)CO(CH_2)_v$-, $R^{7b}CON(R^4)N(R^5)CS(CH_2)_v$-,
$R^4N(OR^{7b})CO(CH_2)_v$- or $R^{7a}CON(OR^{7b})CO(CH_2)_v$-;
and v is as defined above;
R^4, R^{4a}, R^5 are independently hydrogen, phenyl, substituted phenyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, C_3-C_{10} alkenyl, substituted C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, or substituted C_3-C_{10} alkynyl where the substituents on the phenyl, alkyl, alkenyl or alkynyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, phenyl C_1-C_3 alkoxy, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, where the substituents on the phenyl are as defined above, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_1-C_6 alkyl, phenyl, phenyl C_1-C_6 alkyl, C_1-C_5-alkoxycarbonyl or C_1-C_5-alkanoyl-C_1-C_6 alkyl; or
R^4 and R^5 can be taken together to form $-(CH_2)_rB(CH_2)_s$- where B is CH_2, O or $S(O)_m$ or N-R^{10}, r and s are independently 1 to 3, and R^{10} is as defined above;
R^6 is hydrogen, C_1-C_{10} alkyl, phenyl or phenyl C_1-C_{10} alkyl;
A is



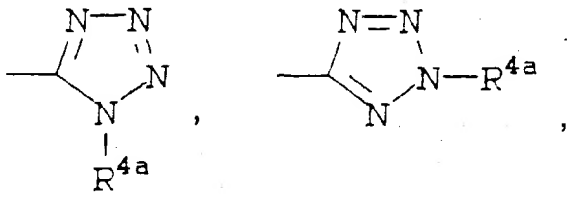
where x and y are independtly 0-3;
R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, trifluoromethlyl, phenyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, phenyl C_1-C_3 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or $-NR^{10}R^{11}$ where R^{10} and R^{11} are as defined above; or
R^8 and R^{8a} can be taken together to form $-(CH_2)_t$- where t is 2 to 6; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

2. A compound of Claim 1 wherein:
n is 0 or 1;
p is 0 to 3;
q is 0 to 2;
w is 0 or 1;
X is 0, S(O)m,

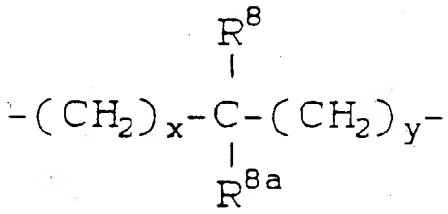


-CH=CH-;
m is 0 to 2;
R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, -$S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;
R^{7a} and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl; phenyl and v is 0 to 2;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9 or phenoxy substituted with R^9;
R^9 is



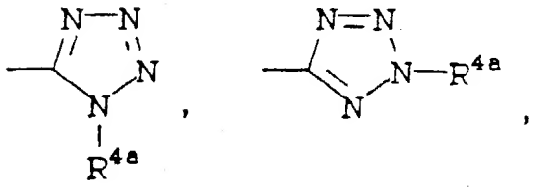
$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, $R^{7b}CO(CH_2)_v$-, $R^4R^5N(CH_2)_v$-, $R^{7b}CON(R^4)(CH_2)_v$-, $R^4R^5NCO(CH_2)_v$-, $R^4R^5NCS(CH_2)_v$, $R^4R^5NN(R^5)CO(CH_2)_v$-, $R^{7b}CON(R^4)N(R^5)CO(CH_2)_v$-, $R^4N(OR^{7b})CO(CH_2)_v$- or $R^{7a}CON(OR^{7b})CO(CH_2)_v$-; where v is as defined above; R^4, R^{4a}, R^5 are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, phenyl C_1-C_3 alkoxy, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, where the substituents on the phenyl are as defined above, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy or formyl;
R^4 and R^5 can be taken together to form $-(CH_2)_rB(CH_2)_s$- where B is CH_2, O or $S(O)_m$ or N-R^{10} r ans s are independently 1 to 3 and R^{10} is as defined above;
R^6 is hydrogen, C_1-C_{10} alkyl or phenyl C_1-C_{10} alkyl;
A is



where x and y are independently 0-2;
R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, phenyl, R^1 substituted or R^1 R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_1-C_6 alkyl, or C_1-C_5 alkanoyl-C_1-C_6 alkyl; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t$- where t is 2 to 4; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

3. A compound of Claim 2 wherein:
n is 0 or 1;
p is 0 to 2;
q is 0 to 2;
w is 0 or 1;
X is $S(O)_m$, -CH=CH-;
m is 0 or 1;
R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;
R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl and v is 0 to 2;
R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9 or phenoxy substituted with R^9;

R^9 is

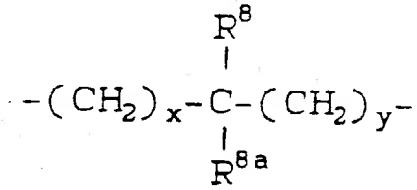


$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, $R^{7b}CO(CH_2)_v$-, $R^4R^5N(CH_2)_v$-, $R^{7b}CON(R^4)(CH_2)_v$-, $R^4R^5NCO(CH_2)_v$-, $R^4R^5NCS(CH_2)_v$, $R^4N(OR^{7b})CO(CH_2)_v$- or $R^{7a}CON(OR^{7b})CO(CH_2)_v$-; where v is as defined above;

R^4, R^{4a}, R^5 are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl, are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, fluoro, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, where the substituents on the phenyl are as defined above, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy;

R^6 is hydrogen, C_1-C_{10} alkyl;

A is



where x and y are independently 0-2;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or

R^8 and R^{8a} can be taken together to form -$(CH_2)_t$- where t is 2; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;

and pharmaceutically acceptable salts thereof.

4. A compound of Claim 3 wherein:

n is 0 or 1;

p is 0 to 2;

q is 1;

w is 1;

X is $S(O)_m$ or -CH=CH-;

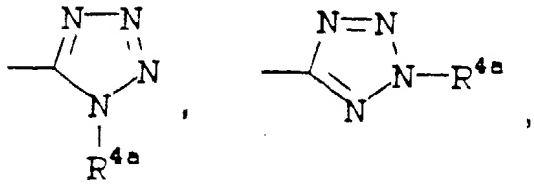
m is 0 or 1;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, -$S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl, phenyl and v is 0 to 1;

R^{3a} and R^{3b} are independently hydrogen or R^9;

R^9 is



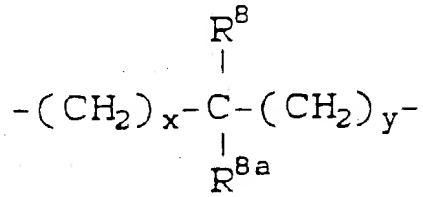
$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, $R^{7b}CO(CH_2)_v$-, $R^4R^5N(CH_2)_v$-, $R^{7b}CON(R^4)(CH_2)_v$-, $R^4R^5NCO(CH_2)_v$- or $R^4N(OR^{7b})CO(CH_2)_v$-; where v is as defined above;

R^4, R^5 are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 3 of hydroxy, C_1-C_3 alkoxy, fluoro, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, where the substituents on the phenyl are as defined above;

R^{4a} is hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents on the alkyl are from 1to 3 of hydroxy.

R^6 is hydrogen;

A is

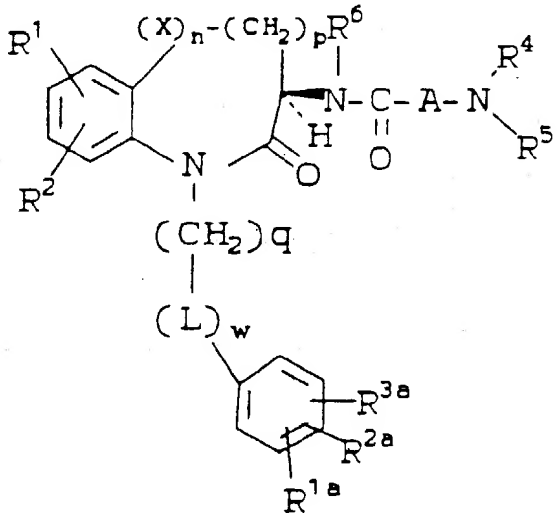


where x and y are independently 0-1;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t$- where t is 2; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;

and pharmaceutically acceptable salts thereof.

5. A stereospecific compound of Claim 1 having the following structural formula:



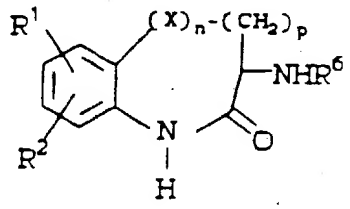
where R^1, R^2, X, n, p, q, L, w, R^{1a}, R^{2a}, R^{3a},R^4, R^5, A and R^6 are as defined in Claim 1

6. A compound of Claim 1 which is:
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide;
2(R)-amino-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide;
2(R)-amino-3-phenyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide;
2(R)-amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide;
3-(2-hydroxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-[1-(2-hydroxyethyl)tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide;
3-(2-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl)methyl]-1H-1-benzazepin-3(R)-yl]-butanamide;
2-amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide;
3-amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide;
3-amino-3-methyl-N-[7-trifluoromethyl-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide;
3-amino-3-methyl-N-[6-fluoro-2,3,4,5-tetrahydro-2-oxo-1-1[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide;
3-benzylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide; or
3-amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide;
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl)-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2(S)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2(R),3-dihydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2(S),3-dihydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(3(S)-hydroxybutyl)amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(3(S)-hydroxybutyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-amino-3-methyl-N-[7-hydroxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl)methyl)-1H-1-benzazepin-3(R)-yl)-butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-hydroxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1-1[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
2-(3(R)-hydroxybutyl)amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide
2-(3(S)-hydroxybutyl)amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide
3-Amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl)-butanamide
3-(3(S)-hydroxybutyl)amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
Quinuclidine-N′-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-3-carboxamide
3-(2-fluoropropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2-methoxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-

yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2-hydroxy-2-methylpropyl)amino-3-methyl-N-[2,-3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
4′-[[3(R)-[[3-[(2(R)-hydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
4′-[[3(R)-[[(3-[(2(S),3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
N-ethyl-4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
N-ethyl-4′-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
N-methyl-4′-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)amino)-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-hydroxymethyl[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-hydroxymethyl[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-aminomethyl[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-aminomethyl[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
4′-[[3(R)-[[3-[(2(S),3(S),4-trihydroxybutyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
4′-[[3(R)-[[3- [(3- hydroxybutyl)amino]- 3- methyl- 1- oxobutyl]amino]- 2,3,4,5- tetrahydro- 2- oxo- 1H- 1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
3-Amino-3-methyl-N-[2,3-dihydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3-dihydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
N-ethyl-4′-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3-dihydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)yl]-butanamide
3-(2(S)-hydroxypropyl)amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(-S)yl]-butanamide
N-ethyl-4′-[[3(S)-[[3-[(2(S),3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-3,4-dihydro-4-oxo-1,5-benzothiazepin-5(2H)-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
4′-[[3(S)-[(3-amino-3-methyl-1-oxobutyl)amino]-3,4-dihydro-4-oxo-1,5-benzothiazepin-5(2H)-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-thioamide
N-hydroxy-4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl]-[1,1′-biphenyl]-2-carboxamide
N-hydroxy-4′-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)amino]-3- methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
N-hydroxy-4′-[[3(R)-[[3-[(2(R)-hydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)yl)-butanamide
3-amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide
3-amino-3-methyl-N-[7-methylthio-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methylthio-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methylsulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-

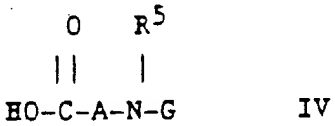
yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-amino-3-methyl-N-[7-methylsulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1[[2′-(acetylaminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(acetylaminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(benzoylaminomethyl)[1,1′-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(benzoylaminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-amino-3-methyl-4-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl)-methyl]-1H-1-benzazepin-3(R)-yl]butanamide
2-Amino-2-methyl-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl)-1H-1-benzazepin-3(R)-yl]propanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-4-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl[1,1′-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3-(R)-yl]-butanamide
2-(3-hydroxybutyl)amino-2-methyl-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo1-[[2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]1H-1-benzazepin-3(R)yl]propanamide
and pharmaceutically acceptable salts of such compounds.

7. A process for the preparation of a compound of Claim 1 which comprises reacting a compound having a formula:



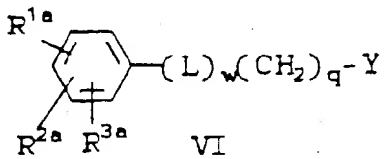
III

where R^1, R^2, R^6, X, n and p are as defined in Claim 1 with a compound having the formula:



IV

where R^5 and A are as defined in Claim 1 and G is a protecting group; which step is either followed by or preceded by the treatment of the compound with

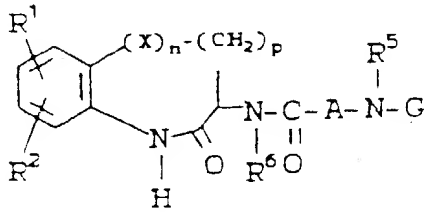


VI

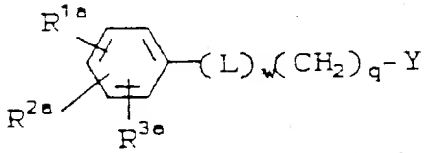
where R^{1a}, R^{2a}, R^{3a}, L, w and q are defined in Claim 1 and Y is a leaving group, followed by the replacement of the protecting group with R^4.

8. The process of Claim 7 where compound III is first reacted with compound IV followed by reaction with compound VI.

9. A process for the preparation of a compound of Claim 1 which comprises reacting a compound having a formula:



where R^1, R^2, R^5, R^6, X, n and p are as defined in Claim 1 and G is a protecting group, with a compound having the formula:



VI

where R^{1a}, R^{2a}, R^{3a}, L, w and q are as defined in Claim 1 and Y is a leaving group, followed by replacement of the protecting group G with R^4.

10. The process of Claim 9 where the protecting group G is t-butoxycarbonyl or benzyloxycarbonyl and L is chlorine, bromine, iodine, O-methanesulfonyl or O-(p-toluenesulfonyl).

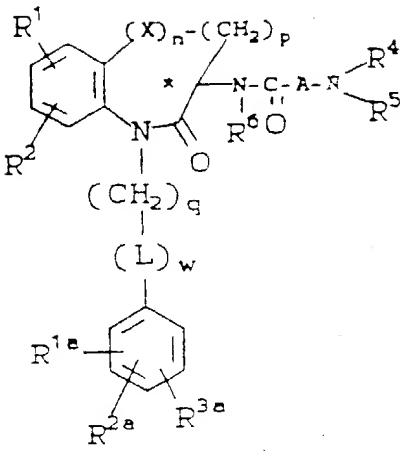
11. The use of a compound of Claim 1 for the manufacture of a medicament for increasing levels of endogenous growth hormone in a human or an animal.

12. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim 1.

13. A composition useful for increasing the endogenous production/release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim 1 used in combination with other growth hormone secretagogues such as, GHRP-6 or GHRP-1, growth hormone releasing factor (GRF) or one of its analogs, IGF-1 or 1GF-2, or B-HT920.

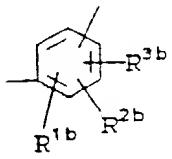
Claims for the following Contracting States: ES, GR

1. A process for the preparation of a compound having the formula :

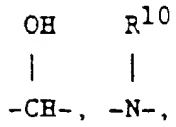


(I)

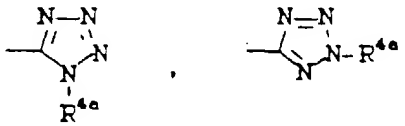
where L is



n is 0 or 1;
p is 0 to 3;
q is 0 to 4;
w is 0 or 1;
X is C=O, O, $S(O)_m$,



-CH=CH-;
m is 0 to 2;
R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_3 perfluoroalkoxy, $-S(O)_mR^{7a}$, cyano, nitro, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;
R^{7a} and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the phenyl substitutents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy and v is 0 to 3; R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9 or phenoxy substituted with R^9;
R^9 is



$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, $R^{7b}CO(CH_2)_v$-, $R^{7b}O(CH_2)_vCO$-, $R^4R^5N(CH_2)_v$-, $R^{7b}CON$

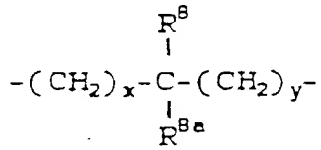
$(R^4)(CH_2)_v$-, $R^4R^5NCO(CH_2)_v$-, $R^4R^5NCS(CH_2)_v$-, $R^4R^5NN(R^5)CO(CH_2)_v$-, $R^4R^5NN(R^5)CS(CH_2)_v$-, $R^{7b}CON(R^4)N(R^5)CO(CH_2)_v$-, $R^{7b}CON(R^4)N(R^5)CS(CH_2)_v$-, $R^4N(OR^{7b})CO(CH_2)_v$- or $R^{7a}CON(OR^{7b})CO(CH_2)_v$-; and v is as defined above;

R^4, R^{4a}, R^5 are independently hydrogen, phenyl, substituted phenyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, C_3-C_{10} alkenyl, substituted C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, or substituted C_3-C_{10} alkynyl where the substituents on the phenyl, alkyl, alkenyl or alkynyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, phenyl C_1-C_3 alkoxy, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, where the substituents on the phenyl are as defined above, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_1-C_6 alkyl, phenyl, phenyl C_1-C_6 alkyl, C_1-C_5-alkoxycarbonyl or C_1-C_5-alkanoyl-C_1-C_6 alkyl; or

R^4 and R^5 can be taken together to form $-(CH_2)_rB(CH_2)_s$- where B is CH_2, O or $S(O)_m$ or N-R^{10}, r and s are independently 1 to 3, and R^{10} is as defined above;

R^6 is hydrogen, C_1-C_{10} alkyl, phenyl or phenyl C_1-C_{10} alkyl;

A is



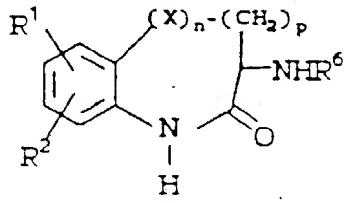
where x and y are independently 0-3;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, trifluoromethyl, phenyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, phenyl C_1-C_3 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or $-NR^{10}R^{11}$ where R^{10} and R^{11} are as defined above; or

R^8 and R^{8a} can be taken together to form $-(CH_2)_t$- where t is 2 to 6; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;

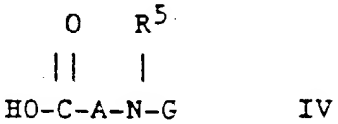
and pharmaceutically acceptable salts thereof;

which process comprises reacting a compound having the formula:



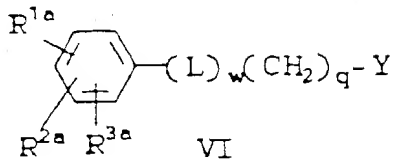
III

where R^1, R^2, R^6, X, n and p are as defined above; with a compound having the formula:



IV

where R^5 and A are ae defined above and G is a protecting group; which step is either followed by or preceded by the treatment of the compound with

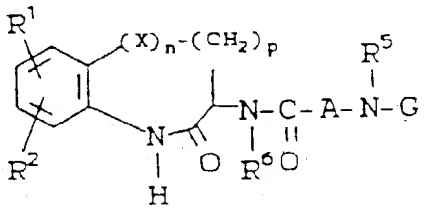


VI

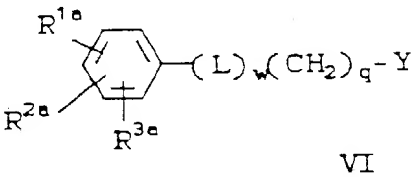
where R^{1a}, R^{2a}, R^{3a}, L, w and q are as defined above and Y is a leaving group; followed by the replacement of the protecting group with R^4.

2. The process of Claim 1 where compound III is first reacted with compound IV followed by reaction with compound VI.

3. A process for the preparation of a compound of formula I as defined in Claim 1 which comprises reacting a compound having the formula:



where R^1, R^2, R^5, R^6, X, n and p are as defined in Claim 1 and G is a protecting group, with a compound having the formula:

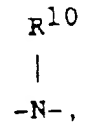


VI

where R^{1a}, R^{2a}, R^{3a}, L, w and q are as defined in Claim 1 and Y is a leaving group, followed by replacement of the protecting group G with R^4.

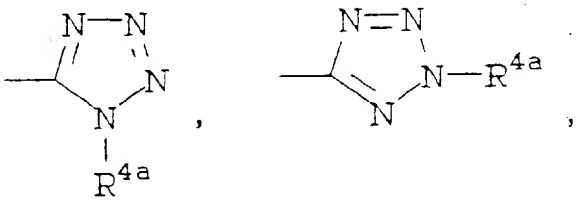
4. The process of Claim 3 where the protecting group G is t-butoxycarbonyl or benzyloxycarbonyl and L is chlorine, bromine, iodine, O-methanesulfonyl or O-(p-toluenesulfonyl).

5. A process as claimed in Claim 1 for the preparation of a compound wherein:
n is 0 or 1;
p is 0 to 3;
q is 0 to 2;
w is 0 or 1;
X is O, $S(O)_m$,

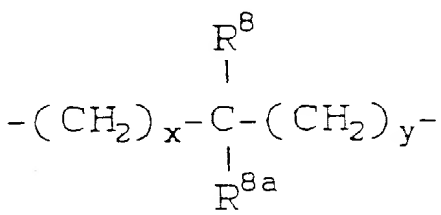


-CH=CH-;
m is 0 to 2;
R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, -

$S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;
R^{7a} and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl; phenyl and v is 0 to 2;
R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9 or phenoxy substituted with R^9;
R^9 is



$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, $R^{7b}CO(CH_2)_v$-, $R^4R^5N(CH_2)_v$-, $R^{7b}CON(R^4)(CH_2)_v$-, $R^4R^5NCO(CH_2)_v$-, $R^4R^5NCS(CH_2)_v$-, $R^4R^5NN(R^5)CO(CH_2)_v$-, $R^{7b}CON(R^4)N(R^5)CO(CH_2)_v$-, $R^4N(OR^{7b})CO(CH_2)_v$- or $R^{7a}CON(OR^{7b})CO(CH_2)_v$-; where v is as defined above; R^4, R^{4a}, R^5 are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, phenyl C_1-C_3 alkoxy, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, where the substituents on the phenyl are as defined above, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy or formyl;
R^4 and R^5 can be taken together to form $-(CH_2)_rB(CH_2)_s$- where B is CH_2, O or $S(O)_m$ or N-R^{10} r and s are independently 1 to 3 and R^{10} is as defined above;
R^6 is hydrogen, C_1-C_{10} alkyl or phenyl C_1-C_{10} alkyl;
A is

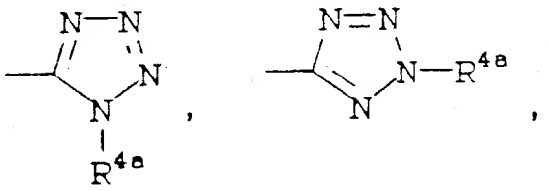


where x and y are independently 0-2;
R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, phenyl, R^1 substituted or R^1 R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_1-C_6 alkyl, or C_1-C_5 alkanoyl-C_1-C_6 alkyl; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t$- where t is 2 to 4; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof

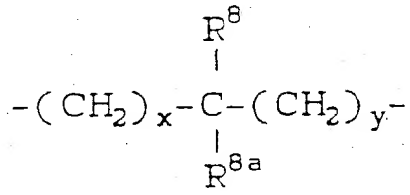
6. A process as claimed in Claim 1 for the preparation of a compound wherein:
n is 0 or 1;
p is 0 to 2;
q is 0 to 2;
w is 0 or 1;
X is $S(O)_m$, -CH=CH-;
m is 0 or 1;
R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, phenyl or substituted phenyl where the substitu-

ents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;
R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl and v is 0 to 2;
R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9 or phenoxy substituted with R^9;
R^9 is

R^9 is

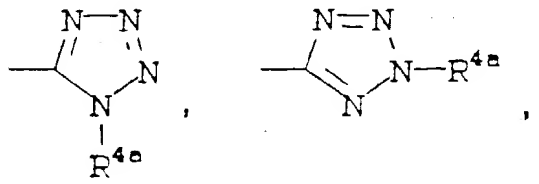


$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, $R^{7b}CO(CH_2)_v$-, $R^4R^5N(CH_2)_v$-, $R^{7b}CON(R^4)(CH_2)_v$-, $R^4R^5NCO(CH_2)_v$-, $R^4R^5NCS(CH_2)_v$-, $R^4N(OR^{7b})CO(CH_2)_v$- or $R^{7a}CON(OR^{7b})CO(CH_2)_v$-; where v is as defined above; R^4, R^{4a}, R^5 are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl, are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, fluoro, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, where the substituents on the phenyl are as defined above, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy;
R^6 is hydrogen, C_1-C_{10} alkyl;
A is



where x and y are independently 0-2;
R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or R^8 and R^{8a} can be taken together to form -$(CH_2)_t$- where t is 2; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

7. A process as claimed in Claim 1 for the preparation of a compound wherein:
n is 0 or 1;
p is 0 to 2;
q is 1;
w is 1;
X is $S(O)_m$ or -CH=CH-;
m is 0 or 1;
R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, -$S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;
R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl, phenyl and v is 0 to 1;
R^{3a} and R^{3b} are independently hydrogen or R^9;
R^9 is



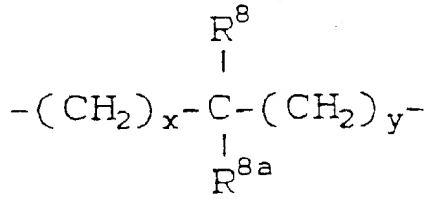
$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, $R^{7b}CO(CH_2)_v$-, $R^4R^5N(CH_2)_v$-, $R^{7b}CON(R^4)(CH_2)_v$-, $R^4R^5NCO(CH_2)_v$-, or $R^4N(OR^{7b})CO(CH_2)_v$- ; where v is as defined above;

R^4, R^5 are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 3 of hydroxy, C_1-C_3 alkoxy, fluoro, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, where the substituents on the phenyl are as defined above;

R^{4a} is hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents on the alkyl are from 1 to 3 of hydroxy.

R^6 is hydrogen;

A is

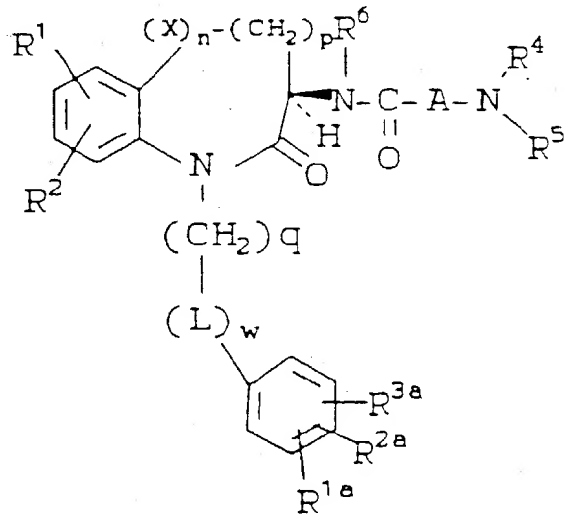


where x and y are independently 0-1;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, phenyl, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or R^8 and R^{8a} can be taken together to form -$(CH_2)_t$- where t is 2; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;

and pharmaceutically acceptable salts thereof.

8. A process as claimed in Claim 1 for the preparation of a compound having the following structural formula:



where R^1, R^2, X, n, p, q, L, w, R^{1a}, R^{2a}, R^{3a}, R^4, R^5, A and R^6 are as defined in Claim 1.

9. A process as claimed in Claim 1 for the preparation of a compound which is:
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide;
2(R)-amino-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide;
2(R)-amino-3-phenyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide;
2(R)-amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide;
3-(2-hydroxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-[1-(2-hydroxyethyl)tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide;
3-(2-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide;
2-amino-2-methyl-N-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl[-4-ylmethyl]-1H-1-benzazepin-3(R)-yl]-propanamide;
3-amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide;
3-amino-3-methyl-N-[7-trifluoromethyl-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide;
3-amino-3-methyl-N-[6-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide;
3-benzylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide; or
3-amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide;
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl[-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2(S)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2(R),3-dihydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2(S),3-dihydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(3(S)-hydroxybutyl)amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(3(S)-hydroxybutyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-amino-3-methyl-N-[7-hydroxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl)methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-hydroxy-2,3,4,5-tetrohydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1-1[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
2-(3(R)-hydroxybutyl)amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide
2-(3(S)-hydroxybutyl)amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide
3-Amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(3(S)-hydroxybutyl)amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
Quinuclidine-N′-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-3-carboxamide
3-(2-fluoropropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-

yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2-methoxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2-hydroxy-2-methylpropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
4′-[[3(R)-[[3-[(2(R)-hydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
4′-[[3(R)-[[(3-[(2(S),3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
N-ethyl-4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
N-ethyl-4′-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]omino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
N-methyl-4′-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)amino)-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyi]-[1,1′-biphenyl]-2-carboxamide
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-hydroxymethyl[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-hydroxymethyl[1,1′-biphenyi]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-aminomethyl[1,1′-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-aminomethyl[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
4′-[[3(R)-[[3-[(2(S),3(S),4-trihydroxybutyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
4′-[[3(R)-[[3-[(3-hydroxybutyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
3-Amino-3-methyl-N-[2,3-dihydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3-dihydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
N-ethyl-4′-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3-dihydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)yl]-butanamide
3-(2(S)-hydroxypropyl)amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)yl]-butanamide
N-ethyl-4′-[[3(S)-[[3-[(2(S),3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-3,4-dihydro-4-oxo-1,5-benzothiazepin-5(2H)-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
4′-[[3(S)-[(3-amino-3-methyl-1-oxobutyl)amino]-3,4-dihydro-4-oxo-1,5-benzothiazepin-5(2H)-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-thioamide
N-hydroxy-4′-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl]-[1,1′-biphenyl]-2-carboxamide
N-hydroxy-4′-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)amino]-3- methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
N-hydroxy-4′-[[3(R)-[[3-[(2(R)-hydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1′-biphenyl]-2-carboxamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)yl]-butanamide
3-amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide
3-amino-3-methyl-N-[7-methylthio-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methylthio-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-

yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methylsulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
3-amino-3-methyl-N-[7-methylsulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(acetylaminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(acetylaminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(benzoylaminomethyl)[1,1′-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(benzoylaminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
3-amino-3-methyl-4-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]butanamide
2-Amino-2-methyl-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]propanamide
3-(2(R)-hydroxypropyl)amino-3-methyl-4-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(1H-tetrazol-5-yl[1,1′-biphenyl)-4-yl]methyl]-1H-1-benzazepin-3-(R)-yl]-butanamide
2-(3-hydroxybutyl)amino-2-methyl-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo1-[[2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]1H-1-benzazepin-3(R)yl]propanamide
and pharmaceutically acceptable salts of such compounds.

10. The use of a compound prepared as described in Claim 1 for the manufacture of a medicament for increasing levels of endogenous growth hormone in a human or an animal.

11. A process for the preparation of a composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises mixing an inert carrier with an effective amount of a compound prepared as described in Claim 1.

12. A process for the preparation of a composition useful for increasing the endogenous production/release of growth hormone in a human or an animal which comprises mixing an inert carrier with an effective amount of a compound prepared as described in Claim 1 used in combination with other growth hormone secretagogues such as, GHRP-6 or GHRP-1, growth hormone releasing factor (GRF) or one of its analogs, IGF-1 or IGF-2, or B-HT920.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 30 2143

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 349 949 (FUJISAWA) * Pages 49-53, claims * ---	1-13	C 07 D 403/10 C 07 D 401/10 C 07 D 227/10 C 07 D 281/10 C 07 D 247/00 C 07 D 283/00 A 61 K 31/33 C 07 D 223/16 C 07 D 417/10 C 07 D 453/02 C 07 D 269/00
A	EP-A-0 166 357 (MERCK) * Pages 54-59, claims * ---	1-13	
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, no. 8, August 1989, pages 1681-1685, American Chemical Society, Washington, DC, US; W.H. PARSONS et al.: "Cholecystokinin antagonists. Synthesis and biological evaluation of 3-substituted benzolactams" * Page 1682, Table I, compound 12 * -----	1-13	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 D 403/00
C 07 D 401/00
C 07 D 281/00
C 07 D 453/00
C 07 D 223/00
C 07 D 417/00
C 07 K 5/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	03-08-1992	LUYTEN H.

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